UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PFIZER INC., PHARMACIA & UPJOHN COMPANY LLC, and PFIZER HEALTH AB, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	**Civil Action No. 07-11198-LTS(KNF)** **ORAL ARGUMENT REQUESTED**

PLAINTIFF PFIZER'S OPPOSITION TO DEFENDANT TEVA'S MOTION TO TRANSFER

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I. INTRODUCTION

The Court should deny Teva Pharmaceuticals USA, Inc.'s ("Teva") motion to transfer this case to the District Court for the District of New Jersey for at least the following reasons. First, a plaintiff's choice of forum should rarely be disturbed, and Pfizer Inc. ("Pfizer") has chosen this District, home of Pfizer's worldwide headquarters, as an appropriate forum. Second, in its transfer analysis, Teva relies entirely on a single factor – judicial efficiency – arguing that the rest are neutral, at best. Transfer will not promote judicial efficiency, however, leaving Teva with no factors in its favor. Third, other factors weigh against transfer. Under these circumstances, Teva cannot meet its burden of showing that transfer is "clearly" warranted.

Pfizer has sued Teva for infringement of three patents that cover Pfizer's Detrol® LA medication. One of those three patents is also at issue in a matter pending in the District of New Jersey. On grounds of that minimal overlap, Teva argues that transfer is appropriate. According to Teva, the District of New Jersey has "experience with the issues," and transfer would allow the parties to avoid duplicative discovery and schedule joint hearings and conferences. In fact, the District Court in New Jersey has no substantive experience with the merits of the single overlapping patent, and that Court has no experience whatsoever with the two patents at issue here but not in New Jersey. Moreover, there would be no duplication of efforts with respect to the single overlapping patent: discovery in the District of New Jersey is all but closed, and the parties have already agreed to treat all earlier discovery as if taken in the present matter, wherever they litigate it. There cannot possibly be duplication of efforts with respect to the two additional patents at issue here, as they were not and will not be litigated in the New Jersey action. Courts generally do not transfer patent cases where the overlap of patents and issues is as limited as it is in this case. For these reasons, the Court should deny Teva's motion to transfer.

II. STATEMENT OF FACTS

A. The Present Action Involves Three Separate Patents

This case concerns three patents: U.S. Patent Nos. 5,382,600 ("'600 patent"), 6,630,162 ("'162 patent"), and 6,770,295 ("'295 patent"). These patents cover different aspects of Pfizer's "Detrol® LA," an extended-release medication approved for treatment of symptoms related to overactive bladder. (Declaration of Adam Gahtan (the "Gahtan Decl."), attached hereto as Exhibit A, ¶ 2.) Broadly, the '600 patent covers a class of chemical compounds that includes tolterodine, the active ingredient in Detrol® LA, and the '162 and '295 patents cover pharmaceutical formulation technology that provides for the sustained release of tolterodine. (Id. ¶¶ 3–5.)

This controversy arose in the context of the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetics Act ("Hatch-Waxman"), which govern, among other things, FDA approval of generic versions of patent-protected drugs. In October 2007, Teva filed an Abbreviated New Drug Application ("ANDA") to market a generic version of Pfizer's Detrol® LA ("LA" indicates "long-acting"). In its LA ANDA, Teva certified as to its belief that the '600, '162, and '295 patents are invalid and unenforceable, and that Teva would not infringe Pfizer's patents by the manufacture, use, or sale of its generic tolterodine product. (Teva's Answer ¶ 18.) Pfizer filed this infringement action upon notice of Teva's certification, invoking an automatic 30-month stay on the FDA's approval of Teva's LA ANDA. 21 U.S.C. § 355(j)(5)(B)(iii).

During the 30-month stay, the FDA may not approve Teva's Detrol® LA ANDA unless Teva proves that its manufacture, use, sale, or offer to sell its proposed generic product will not infringe any valid, enforceable claim of any of the '600, '162, and '295 patents. 21 U.S.C. § 355(j)(5)(B)(iii)(I)–(II). If Teva does not prevail with respect to all patents, the FDA may not approve Teva's LA ANDA until expiration of the last-to-expire of the infringed patents. The

'600 patent will expire on September 25, 2012; the '162 and '295 patents will expire on May 11, 2020, and February 26, 2020, respectively. (Gahtan Decl. ¶ 2.) Accordingly, if the Court determines that Teva infringes even one valid, enforceable claim of either the '162 or '295 patents, the FDA may not approve Teva's LA ANDA until 2020, at the earliest, regardless of any decision with respect to the '600 patent.

B. Earlier Litigation Concerned the '600 Patent Only

The matter pending in the District of New Jersey concerns a separate product. In addition to Detrol LA®, Pfizer sells an immediate-release (IR) tolterodine product under the trade name "Detrol®." Only the '600 patent covers the IR product; the '162 and '295 patents do not. (Id. ¶¶ 2, 6.) In February 2004, Teva filed a separate ANDA to market a generic version of the IR product, certifying as to its belief that the '600 patent is invalid or unenforceable. (Id. ¶ 7.) On March 26, 2004, Pfizer sued Teva for infringement of the '600 patent in the United States District Court for the District of New Jersey. (See id.)

In January 2006, Teva acquired IVAX Pharmaceuticals ("IVAX"). IVAX had previously filed its own tolterodine IR ANDA, which did not contain a certification that the '600 patent is invalid or unenforceable, and so did not lead to litigation between Pfizer and IVAX. (Id. ¶ 8.) In January 2007, after three years of litigation and just before summary judgment briefs were due, Teva withdrew its IR ANDA and amended the IVAX ANDA to include an invalidity/unenforceability certification identical to Teva's. (Id.) Teva's decision resulted in dismissal of the first action (as Teva no longer sought to market a generic product, there was no jurisdiction under Hatch-Waxman), in favor of a new action against IVAX. That action is pending in the District of New Jersey (C.A. No. 07-0174 (DMC)(MF)). Because the '162 and

'295 patents do not cover Pfizer's IR Detrol® product, those patents have never been the subject of discovery or other proceeding in either action in the District of New Jersey.

The parties to the IVAX action (which Teva joined) stipulated that all discovery taken in the Teva action would apply as if taken in the IVAX action. (Id. ¶ 9.) With the exception of IVAX's production of a few additional documents, expected by February 1, 2008, and possible supplemental expert reports, discovery is closed in the IVAX action. (Teva's Br. 4.) Under the most recent schedule, IVAX was to have finished its production by December 21, 2007. (Declaration of James S. Trainor, Jr., attached hereto as Exhibit B, ¶¶ 2–5.) Because IVAX's production is still incomplete, the parties have agreed that the March 7, 2008 summary judgment due date – to which Teva repeatedly refers – will be postponed. (Id.)

C. The District Court in New Jersey Has Had No Occasion to Become Substantively Familiar with the Technology in the '600 Patent

In the nearly four years of the Teva/IVAX litigations in the District of New Jersey, the parties have never been before Judge Cavanaugh, who will make all substantive decisions. (Gahtan Decl. ¶ 9.) To date, there has been no decision on any aspect of the merits with respect to the '600 patent, the Court has heard no fact or expert testimony, nor taken any other evidence, about the '600 patent, there are no merit-related motions pending, there has been no tutorial about the technology, and trial has never been scheduled. (Id.)

III. ARGUMENT

A district court may transfer a case to another district for the convenience of the parties and witnesses, or in the interest of justice. 28 U.S.C. § 1404(a). Courts afford deference to plaintiff's choice of forum, and the moving party bears the burden of establishing, by clear and convincing evidence, that the court should transfer the case. American Steamship Owners Mut. Prot. & Indem. Assoc., Inc. v. LaFarge N.A., Inc., 474 F. Supp. 2d 474, 480 (S.D.N.Y. 2007);

Pall Corp. v. PTI Techs., Inc., 992 F. Supp. 196, 198 (E.D.N.Y. 1998). Teva cannot carry that burden here.

This Court weighs up to nine factors in deciding whether to transfer an action:

> (1) the convenience of witnesses; (2) the location of relevant documents and the relative ease of access to sources of proof; (3) the convenience of the parties; (4) the locus of the operative facts; (5) the availability of process to compel attendance of unwilling witnesses; (6) the relative means of the parties; (7) a forum's familiarity with the governing law; (8) the weight accorded a plaintiff's choice of forum; (9) trial efficiency and the interests of justice, based on the totality of the circumstances.

Aerotel Ltd. v. Sprint Corp., 100 F. Supp. 2d 189, 196 (S.D.N.Y. 2000). Teva rests its motion entirely on judicial economy, which is a subset of a single factor – efficiency. (Teva's Br. 6–8.) Teva concedes that the remaining factors do not support its motion. (Id. 2.) Teva argues that transfer "will facilitate judicial efficiency by taking advantage of the District of New Jersey's experience with the issues between the parties, avoiding duplicative discovery, and permitting the scheduling of joint hearings and conferences as appropriate." (Id. 1–2.)

Teva is incorrect. First, courts will not transfer patent cases to districts in which somewhat related cases are pending unless there is greater overlap of the patents and issues than there is here. Two of the three patents in the present case have no place at all in the New Jersey action, and no decision in the New Jersey action can result in approval of Teva's LA ANDA. Second, there will be no gains in judicial efficiency. Discovery is all but closed with respect to the only common issue, the '600 patent, and the parties have already agreed – as they have in the past – to apply all discovery relating to the '600 patent to the new dispute, wherever it is heard. Moreover, there has never been discovery or other proceedings with respect to the '162 or '295 patents in the New Jersey action. Finally, a plaintiff's choice of forum should rarely be disturbed. This Court should deny Teva's motion.

A. There is Insufficient Overlap of Issues to Warrant Transfer

Courts will deny motions to transfer where the products, technologies, or patents in-suit are different from those at issue in the proposed transferee forum. See Pall, 992 F. Supp. at 201–02 (refusing transfer where different patents covering same technology were at issue in both cases); Connectel, LLC, v. Cisco Systems, Inc., No. 2:04-CV-396, 2005 WL 366966, at *1, 3–4 (E.D. Tex. Feb. 16, 2005) (no transfer to court that previously considered only one of four patents at issue); Datamize, Inc. v. Fidelity Brokerage Servs., LLC, No. 2:03-CV-321-DF, 2004 WL 1683171, at *12 (E.D. Tex. Sept. 5, 2003) (no transfer because, "[a]lthough the actions involve parent and child patents having identical specifications, drawings, and inventors," the patent claims were "substantially different"); SmithKline Beecham Corp. v. Geneva Pharms., Inc., No. Civ.A. 99-CV-2926, 2000 WL 217642, at *2 (E.D. Pa. Feb. 11, 2000) (no transfer where pending action involved only one of the three patents in-suit).

The facts of SmithKline are nearly identical to those before the Court. The patentee sued a generic pharmaceutical manufacturer following the filing of a ANDA that contained a certification that three patents covering patentee's drug were invalid. SmithKline, 2000 WL 217642, at *1. The defendant moved to transfer the case to the Northern District of Illinois, where the patentee had already asserted one of the three patents against another generic manufacturer. Id. The Court denied the motion because the case "involve[d] two other patents which are not at issue in the Illinois litigation." Id. at *2. The generic defendant's assertion that the products in the two cases "must be similar, even identical," failed to persuade the court that transfer was warranted. Id. Moreover, discovery was closed in the parallel litigation, which according to the SmithKline court, "diminish[ed] the possibility of consolidation or coordination to promote judicial economy." Id. at *2.

Here, as in SmithKline, the case arises under Hatch-Waxman, only one of the three patents-in-suit in this case is the subject of litigation in another jurisdiction, and discovery in the action in the proposed transferee forum is effectively closed. Because "the possibility of consolidation or coordination" is likewise "diminish[ed]" by these two indisputable facts, this Court should deny transfer.

Teva cites cases that support only the general proposition that patent suits may be transferred "where litigation involving the same patent [is] ongoing in another jurisdiction" (Teva's Br. 5–6), but it overlooks courts' routine refusal, discussed above, to transfer in the absence of complete overlap. All but two of the decisions that Teva relies on involved complete overlap of the patents in-suit in the transferor and transferee courts,[1] and Teva's remaining authority is readily distinguishable. In Zoltar Satellite Systems., Inc. v. LG Electronics Mobile Communications Co., 402 F. Supp. 2d 731 (E.D. Tex. 2005), four patents were before the transferor court, three of which were also before the transferee court. Id. at 736. The Court granted transfer because plaintiff was unable to "identify specific significant differences between the technology at issue" in the cases, and because the transferee court had already (1) received tutorials on the technology at issue, (2) issued three claim construction orders, (3) considered the motions for summary judgment, and (4) presided over a jury trial involving invalidity, infringement and inequitable conduct issues. Id. at 735–36. Here, in contrast, the District Court in New Jersey has had no occasion to take evidence or consider briefs on the merits of the '600

[1] See Encyclopedia Britannica, Inc. v. Magellan Navigation, Inc., 512 F. Supp. 2d 1169 (W.D. Wisc. 2007) ("exact same patents" were already subject of litigation in transferee forum); Aventis Pharma S.A. v. Sandoz Inc., Civil Action No. 06-3671 (MLC), 2007 WL 1101228, at *1 (D.N.J. Apr. 10, 2007) (plaintiff "filed complaints raising identical claims of patent infringement" against defendant on same day in two districts); Air Products & Chem., Inc. v. MG Nitrogen Servs., Inc., 133 F. Supp. 2d 354, 357 (D. Del. 2001); B.W.B. Controls, Inc. v. C.S.E. Automation Engineering & Servs., Inc., 587 F. Supp. 1027, 1028 (W.D. La 1984) (plaintiff "has brought two other infringement claims involving these patents" and defendant sought declaratory judgment "in regard to the same patents" before the same judge in another district); E.I. DuPont de Nemours & Co. v. Diamond Shamrock Corp., 522 F. Supp. 588, 591 (D. Del. 1981).

patent, let alone rule on the merits in any respect, and the technology is different: the '600 patent relates to the active ingredient in Detrol® and Detrol LA®, and the '162 and '295 patents relate to formulations that provide for the release of the active ingredient according to certain parameters.

In Imagepoint Inc. v. Keyser Indus., Inc., No. 3:04-CV-119, 2005 WL 1242067 (E.D. Tenn. May 25, 2005), plaintiff conceded that it planned to amend its claims in the transferee forum to include all of the patents at issue in the transferor court, if transfer were granted. Id. at *2. In contrast, Pfizer could not amend its complaint in the New Jersey action to include the '162 or '295 patents, as those patents have no bearing on the IVAX IR ANDA, which is the sole basis for jurisdiction in that matter. Any suit based on Teva's LA ANDA in the District of New Jersey would be separate from the pending case there because, among other reasons, the statutory 30-month stays start at dates nearly a year apart. Imagepoint is inapposite. Id.

B. Transfer Will Not Promote Judicial Economy

In arguing that transfer "will facilitate judicial efficiency by taking advantage of the District of New Jersey's experience with the issues between the parties, avoiding duplicative discovery, and permitting the scheduling of joint hearings and conferences as appropriate," (Teva's Br. 1–2), Teva focuses on the '600 patent only, ignoring the '162 and '295 patents almost entirely. Teva also mischaracterizes the overlapping '600 patent as "the principal patent" in this action. (Id. 1.) It is indisputable, moreover, that the New Jersey District Court has no "experience with the issues" surrounding the '162 and '295 patents, as they are totally irrelevant to the issues there.

1. The '162 and '295 Patents Are Critical in *This* Dispute

The '162 and '295 patents, which cover the long-acting, extended release Detrol® LA product, are not at issue in the New Jersey action, which involves only an IR ANDA and the

'600 patent. The two additional patents are critical to FDA approval of Teva's LA ANDA, however, which is at issue here: the FDA will not approve Teva's LA ANDA prior to the expiration of any of the '600, '162, or '295 patents unless Teva proves that it does not infringe any valid, enforceable claim in any of the three patents. If Teva prevails with respect to the '600 patent (either here or in New Jersey), but is found to infringe even one valid claim of either of the '162 or '295 patents, then the FDA will not approve Teva's LA ANDA until expiration of the infringed patent(s), both of which expire later than the '600 patent.

2. There Will be No Duplication of Effort Should The Court Maintain Jurisdiction

The parties have already demonstrated their ability to avoid duplicating work when it comes to the '600 patent. When Teva dropped its own IR ANDA and substituted IVAX's, necessitating a new action in the District of New Jersey, the parties agreed to apply all earlier fact and expert discovery to the new action. (Gahtan Decl. ¶ 9.) Counsel for the parties have already agreed that it will be necessary to reach the same agreement for this matter, wherever it is ultimately heard. (Id. ¶ 10.) With the exception of a few remaining documents that IVAX expects to produce on February 1, and the possible exchange of supplemental expert reports, discovery in the New Jersey action is closed. These factors weigh against transfer. See SmithKline, 2000 WL 217642, at *2 (refusing to transfer patent infringement case in part because discovery was already complete in proposed transferee forum). Moreover, as there has been no need for discovery about the '162 or '295 patents in the New Jersey action, the parties will be starting from scratch wherever they litigate this matter; there will be no duplication.

Also contrary to Teva's claims (Teva's Br. 6), the District Court in New Jersey has no head-start on the technology even of the lone overlapping patent. In nearly four years of litigation – the last year of which was courtesy of Teva's decision to substitute one ANDA for

another – the parties have appeared only on discovery-related issues. Judge Cavanaugh, who alone will decide all merits-based issues, has had no opportunity to become familiar with the '600 patent during the parties' complex discovery and as a result of Teva's decision to replace one ANDA with another on the eve of summary judgment in the first IR action. Indeed, the parties have never appeared before Judge Cavanaugh. The parties have not briefed any claim construction or summary judgment motions, they have presented no fact or expert testimony in any sort of hearing, there has been no tutorial about the technology, and there is no date set for trial. Thus, the Court in the District of New Jersey is not substantively familiar with the technology at issue in this case.

Because the parties have agreed to apply earlier discovery to this new dispute, because the New Jersey District Court has no familiarity at all with the '162 and '295 patents, and because it has never had the opportunity to consider any technical issue surrounding the '600 patent in earnest, transfer to the District of New Jersey will not promote judicial economy.

C. **Plaintiff's Choice of Forum and Other Factors Weigh Against Transfer**

A plaintiff's choice of forum is entitled to deference. American Steamship Owners, 474 F. Supp. 2d at 480. Indeed, courts are reluctant to transfer a case absent a showing that "the balance of convenience and justice weighs heavily in favor of transfer." Pall, 992 F. Supp. at 200 (quoting Somerville v. Major Exploration, Inc., 576 F.Supp. 902, 908 (S.D.N.Y. 1983)).

In addition, this District is more convenient for both parties to some degree. Teva will inevitably request that Pfizer produce documents and testimony related to the sales and marketing of Detrol® LA and possibly other products, as well. The witnesses competent to testify about those subjects work at Pfizer's headquarters, which are in this District, and this is where Pfizer generates and maintains the relevant documents. Furthermore, both Pfizer's and Teva's counsel in this action have offices in the Southern District, obviating the need for either

party to hire local counsel, as they were required to do in the District of New Jersey. Pfizer recognizes that litigating in New Jersey would not be a hardship for either party, but these private interest factors are part of the analysis, and they favor maintaining this action in this District.

Teva supports its motion for transfer entirely on the single ground of judicial economy. (Teva's Br. 2.) Pfizer has demonstrated that transfer will not promote judicial economy. See supra Section B. Teva has failed to carry its burden of clearly demonstrating that transfer is warranted. American Steamship Owners, 474 F. Supp. 2d at 480; Pall, 992 F. Supp. at 198. Pfizer's choice of forum should not be disturbed.

IV. CONCLUSION

For the foregoing reasons, Pfizer respectfully requests that the court DENY Teva's motion to transfer.

Dated: January 31, 2008
New York, New York

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UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PFIZER INC., PHARMACIA & UPJOHN COMPANY LLC, and PFIZER HEALTH AB,.	**Civil Action No. 07-11198-LTS(KNF)**
Plaintiff,	**DECLARATION OF ADAM GAHTAN**
v.	
TEVA PHARMACEUTICALS USA, INC.,	
Defendant.	

I, Adam Gahtan, declare as follows:

1. I am an attorney at law duly authorized and admitted to practice law before this Court. I am a partner with the law firm of White & Case LLP, counsel for Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB ("Pfizer"). I have knowledge of the facts set forth in this Declaration and, if called as a witness, could competently testify to these facts.

2. Attached hereto as **Exhibit 1** is a true and correct copy of an excerpt from the 2007 edition of the U.S. Food and Drug Administration's publication "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly known as the "Orange Book." The Orange Book lists all patents claimed by the relevant entity to cover a listed drug. See Orange Book p. v. The Orange Book lists the '600, '162, and '295 patents as covering Detrol® LA. Id. p. ADA 141. The '600 patent will expire on September 25, 2012, while the '162 and '295 patents will expire roughly eight years later, on May 11, 2020, and February 26, 2020, respectively. Id.

3. Attached hereto as **Exhibit 2** is a true and correct copy of U.S. Patent No. 5,382,600 (the "'600 patent"), which is directed to a class of chemical compounds that includes tolterodine. U.S. Patent No. 5,382,600, at [57] (filed Dec. 19, 1991).

4. Attached hereto as **Exhibit 3** is a true and correct copy of U.S. Patent No. 6,630,162 (the "'162 patent"), which is directed to controlled release pharmaceutical formulations for administering tolterodine and the medical use of such formulations. U.S. Patent No. 6,630,162, at [57] (filed Nov. 9, 2000).

5. Attached hereto as **Exhibit 4** is a true and correct copy of U.S. Patent No. 6,770,295 (the "'295 patent"), which is directed to improved methods and formulations for treating overactive bladder with tolterodine. U.S. Patent No. 6,770,295, at [57] (filed Aug. 26, 1999).

6. The Orange Book lists only the '600 patent as covering Detrol.® Orange Book p. ADA 141.

7. Attached hereto, as **Exhibit 5**, is a true and correct copy of Teva's answer filed in Pfizer, Inc. v. Teva Pharms. USA, Inc., No. 04-1418 (DMC) (D.N.J. 2004) (the "First Answer"). In February 2004, Teva Pharmaceuticals USA, Inc. ("Teva") filed an ANDA to market its own immediate release ("IR") tolterodine product. (First Answer ¶ 15.) Teva's IR ANDA included a certification as to Teva's belief that the '600 patent is invalid or unenforceable. (Id. ¶ 17–18.) Consequently, on March 26, 2004, Pfizer sued Teva for infringement of the '600 patent in the United States District Court for the District of New Jersey. (See id.)

8. Attached hereto, as **Exhibit 6**, is a true and correct copy of Pfizer's Reply and Counterclaims filed in Pfizer, Inc. v. Teva Pharms. USA, Inc., No. 07-0174 (DMC)(MF) (D.N.J. 2007) ("Pfizer's IVAX Reply"). In January 2006, Teva acquired IVAX Pharmaceuticals ("IVAX"). (See Pfizer's IVAX Reply p. 17, ¶¶ 21–22.) IVAX also owned an ANDA for an immediate-release tolterodine product, but IVAX's ANDA did not contain a certification that the '600 patent was invalid or unenforceable. (See id. pp. 16–17, ¶¶ 17–19.) In January 2007, just before the parties were scheduled to submit motions for summary judgment, Teva withdrew its IR ANDA and amended IVAX's ANDA to include a certification that the '600 patent is invalid or unenforceable. (See id.)

9. After the IVAX action was filed, the parties agreed that all discovery taken in the Teva action would be treated as taken in the IVAX action. The parties have never appeared before Judge Cavanaugh in the IVAX action, and the New Jersey court has never considered any aspect of the merits with respect to the '600 patent. There are no merit-related motions pending, and there is no trial scheduled.

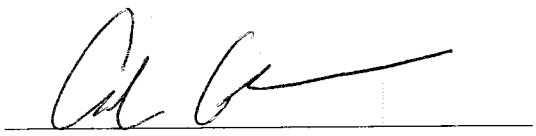
10. On January 10, 2008, I spoke with Don Kennedy of Goodwin Procter LLP, who represents Teva in this matter. Mr. Kennedy and I agreed that the parties would not duplicate discovery with respect to the '600 patent, and that all discovery taken in the District of New Jersey regarding the '600 patent will be treated as taken in this matter wherever it is ultimately litigated.

11. Attached hereto, as **Exhibit 7**, is a true and correct copy of Connectel, LLC, v. Cisco Systems, Inc., No. 2:04-CV-396, 2005 WL 366966 (E.D. Tex. Feb. 16, 2005).

12. Attached hereto, as **Exhibit 8**, is a true and correct copy of Datamize, Inc. v. Fidelity Brokerage Servs., LLC, No. 2:03-CV-321-DF, 2004 WL 1683171 (E.D. Tex. Sept. 5, 2003).

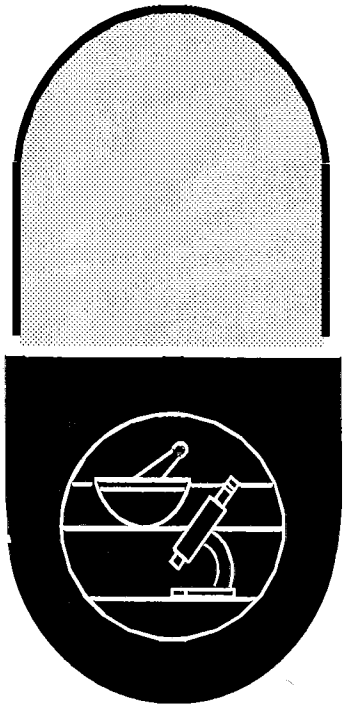
13. Attached hereto, as **Exhibit 9**, is a true and correct copy of SmithKline Beecham Corp. v. Geneva Pharms., Inc., No. Civ.A. 99-CV-2926, 2000 WL 217642 (E.D. Pa. Feb. 11, 2000).

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this Declaration was executed in New York, New York on January 31, 2008.



Adam Gahtan

EXHIBIT 1



APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

27th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2007

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
APPROVED DRUG PRODUCTS
with
Therapeutic Equivalence Evaluations

PREFACE TO TWENTY EIGHTH EDITION

The publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the List, commonly known as the Orange Book), identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act (the Act). Drugs on the market approved only on the basis of safety (covered by the ongoing Drug Efficacy Study Implementation [DESI] review [e.g., Donnatal® Tablets and Librax® Capsules] or pre-1938 drugs [e.g., Phenobarbital Tablets]) are not included in this publication. The main criterion for the inclusion of any product is that the product is the subject of an application with an effective approval that has not been withdrawn for safety or efficacy reasons. Inclusion of products on the List is independent of any current regulatory action through administrative or judicial means against a drug product. In addition, the List contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs. Therapeutic equivalence evaluations in this publication are not official FDA actions affecting the legal status of products under the Act.

Background of the Publication. To contain drug costs, virtually every state has adopted laws and/or regulations that encourage the substitution of drug products. These state laws generally require either that substitution be limited to drugs on a specific list (the positive formulary approach) or that it be permitted for all drugs except those prohibited by a particular list (the negative formulary approach). Because of the number of requests in the late 1970s for FDA assistance in preparing both positive and negative formularies, it became apparent that FDA could not serve the needs of each state on an individual basis. The Agency also recognized that providing a single list based on common criteria would be preferable to evaluating drug products on the basis of differing definitions and criteria in various state laws. As a result, on May 31, 1978, the Commissioner of the Food and Drug Administration sent a letter to officials of each state stating FDA's intent to provide a list of all prescription drug products that are approved by FDA for safety and effectiveness, along with therapeutic equivalence determinations for multisource prescription products.

The List was distributed as a proposal in January 1979. It included only currently marketed prescription drug products approved by FDA through new drug applications (NDAs) and abbreviated new drug applications (ANDAs) under the provisions of Section 505 of the Act.

The therapeutic equivalence evaluations in the List reflect FDA's application of specific criteria to the multisource prescription drug products on the List approved under Section 505 of the Act. These evaluations are presented in the form of code letters that indicate the basis for the evaluation made. An explanation of the code appears in the *Introduction*.

A complete discussion of the background and basis of FDA's therapeutic equivalence evaluation policy was published in the *Federal Register* on January 12, 1979 (44 FR 2932). The final rule, which includes FDA's responses to the public comments on the proposal, was published in the *Federal Register* on October 31, 1980 (45 FR 72582). The first publication, October 1980, of

the final version of the List incorporated appropriate corrections and additions. Each subsequent edition has included the new approvals and made appropriate changes in data.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act (1984 Amendments). The 1984 Amendments require that FDA, among other things, make publicly available a list of approved drug products with monthly supplements. The *Approved Drug Products with Therapeutic Equivalence Evaluations* publication and its monthly Cumulative Supplements satisfy this requirement. The *Addendum* to this publication identifies drugs that qualify under the 1984 Amendments for periods of exclusivity (during which ANDAs or applications described in Section 505(b)(2) of the Act for those drugs may not be submitted for a specified period of time and, if allowed to be submitted, would be tentatively approved) and provides patent information concerning the listed drugs which also may delay the approval of ANDAs or Section 505(b)(2) applications. The *Addendum* also provides additional information that may be helpful to those submitting a new drug application to the Agency.

The Agency intends to use this publication to further its objective of obtaining input and comment on the publication itself and related Agency procedures. Therefore, if you have comments on how the publication can be improved, please send them to the Director, Division of Labeling and Program Support, HFD-610, Office of Generic Drugs, Center for Drug and Evaluation and Research, 7500 Standish Place, Rockville, MD 20855. Comments received are publicly available to the extent allowable under the Freedom of Information regulations.

PRESCRIPTION AND OTC DRUG PRODUCT PATENT AND EXCLUSIVITY LIST

See report footnote for information regarding report content

APPL/PROD NO	PATENT NO	PATENT EXPIRATON DATE	PATENT CODES			EXCLUSIVITY CODE(S)	EXCLUSIVITY EXPIRATION DATE
TIZANIDINE HYDROCHLORIDE; ZANAFLEX							
021447 001	6455557	Nov 28, 2021					
TIZANIDINE HYDROCHLORIDE; ZANAFLEX							
021447 002	6455557	Nov 28, 2021					
TIZANIDINE HYDROCHLORIDE; ZANAFLEX							
021447 003	6455557	Nov 28, 2021					
TOLCAPONE; TASMAR							
020697 001	5236952	Jan 29, 2012					
	5476875	Dec 19, 2012			U-219		
TOLCAPONE; TASMAR							
020697 002	5236952	Jan 29, 2012					
	5476875	Dec 19, 2012			U-219		
TOLTERODINE TARTRATE; DETROL							
020771 001	5382600	Mar 25, 2012					
	5382600*PED	Sep 25, 2012					
TOLTERODINE TARTRATE; DETROL							
020771 002	5382600	Mar 25, 2012					
	5382600*PED	Sep 25, 2012					
TOLTERODINE TARTRATE; DETROL LA							
021228 001	5382600	Mar 25, 2012				M-46	Oct 21, 2008
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	6630162	Nov 11, 2019		DP	U-544		
	6630162*PED	May 11, 2020					
	6770295	Aug 26, 2019		DP	U-544		
	6770295*PED	Feb 26, 2020					
	6911217	Aug 26, 2019		DP	U-544		
	6911217*PED	Feb 26, 2020		DP	U-544		
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	6770295*PED	Feb 26, 2020					
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TOPIRAMATE; TOPAMAX							
020505 001	4513006	Sep 26, 2008	DS	DP	U-83	D-88	Dec 16, 2006
	5998380	Oct 13, 2015			U-598	I-467	Jun 29, 2008
	6503884	Oct 13, 2015			U-598	I-41	Aug 11, 2007
	7018983	Oct 13, 2015			U-723	ODE	Aug 28, 2008
TOPIRAMATE; TOPAMAX							
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	5998380	Oct 13, 2015			U-598	I-467	Jun 29, 2008
	6503884	Oct 13, 2015			U-598	I-41	Aug 11, 2007
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TOPIRAMATE; TOPAMAX							
020505 003	4513006	Sep 26, 2008	DS	DP	U-83	D-88	Dec 16, 2006
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TOPIRAMATE; TOPAMAX							
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	5998380	Oct 13, 2015			U-598	I-467	Jun 29, 2008
	6503884	Oct 13, 2015			U-598	I-41	Aug 11, 2007
	7018983	Oct 13, 2015			U-723	ODE	Aug 28, 2008

EXHIBIT 2

US005382600A

United States Patent [19]

Jönsson et al.

[11] Patent Number: 5,382,600

[45] Date of Patent: Jan. 17, 1995

[54] **3,3-DIPHENYLPROPYLAMINES AND PHARMACEUTICAL COMPOSITIONS THEREOF**

[75] Inventors: **Nils A. Jönsson**, Södertälje; **Bengt A. Sparf**, Trångsund; **Lembit Mikiver**, Järna; **Pinchas Moses**, Saltsjö-Boo; **Lisbet Nilvebrant**, Bromma; **Gunilla Glas**, Spånga, all of Sweden

[73] Assignee: **Pharmacia Aktiebolag**, Uppsala, Sweden

[21] Appl. No.: **810,185**

[22] Filed: **Dec. 19, 1991**

Related U.S. Application Data

[63] Continuation of Ser. No. 543,767, Sep. 24, 1990, abandoned.

[30] **Foreign Application Priority Data**

Jan. 22, 1988 [SE] Sweden 8800207-6

[51] **Int. Cl.**[6] **A61K 31/135**; A61K 31/165; A61K 31/18; C07C 217/62

[52] **U.S. Cl.** **514/603**; 514/620; 514/648; 564/86; 564/165; 564/316

[58] **Field of Search** 564/86, 165, 316; 514/603, 620, 648

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,446,901 5/1969 Jones 424/330

FOREIGN PATENT DOCUMENTS

111894 3/1969 Denmark .
1169944 11/1969 United Kingdom .
1169945 11/1969 United Kingdom .

OTHER PUBLICATIONS

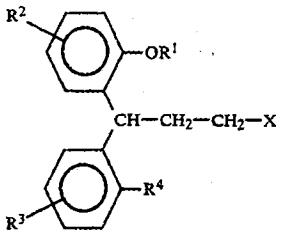
Markaryan et al., Chemical Abstracts, vol. 97 (1982) 120105n.

Atwal et al., J. Med. Chem., vol. 30 (1987) pp. 627–365.

Strehlke et al., Chemical Abstracts, vol. 91 (1979) 107943r.

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Pollock, Vande Sande & Priddy

[57] **ABSTRACT**



(I)

Novel 3,3-diphenylpropylamines of formula (I) wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group $-NR^5$, R^6, wherein R^5 and R^6 signify non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and which may form a ring together with the amine nitrogen, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers, their use as drugs, especially as anticholinergic agents, their use for preparing an anticholinergic drug, pharmaceutical compositions containing the novel amines, and methods for preparing the same.

7 Claims, No Drawings

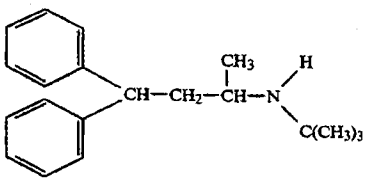
3,3-DIPHENYLPROPYLAMINES AND PHARMACEUTICAL COMPOSITIONS THEREOF

This is a continuation of Ser. No. 07/543,767, filed on Sep. 24, 1990, now abandoned.

The present invention relates to novel 3,3-diphenylpropylamino derivatives, to pharmaceutical compositions containing the same, and to the use of said derivatives for preparing drugs.

Swedish Pat. No. 215 499 discloses certain 3,3-diphenylpropylyamines having an advantageous effect on the heart and circulation. These pharmacologically active 3,3-diphenylpropylamines are secondary amines. Said Swedish patent also discloses certain chemical intermediates which are tertiary amines carrying aromatic substituents on the amine nitrogen. Neither the end products (secondary amines) nor the intermediates (tertiary amines) have any hydroxy or methoxy groups as substituents in the ortho positions of the phenyl rings, but only meta and para substituents are specifically disclosed.

It is known that terodiline, a commercially available drug having the chemical formula

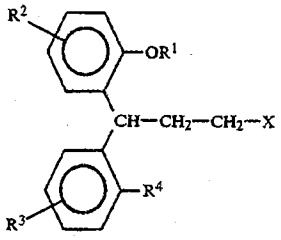


has anti-cholinergic properties, and is well resorbed in the body. However, this drug has a very long biological half-life and it is a multi-effect drug also having other pharmacological properties such as Ca-antagonist, noradrenaline antagonist and anti-histamine properties as well as a pronounced effect on the heart.

U.S. Pat. No. 3,446,901, GB-A-1.169.944 and GB-A-1.169.945 disclose certain 3,3-diphenylpropylamine derivatives and pharmaceutical compositions having antidepressant activity, i.a. N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, which is considered to be the closest prior art as regards chemical structure (see also the comparative tests reported at the end of this specification). DK-A-111.894 discloses a special process for preparing certain diphenylalkylamines having an effect on the heart and circulation. The specifically described compounds are primary or secondary amines, and none of them has any hydroxy or alkoxy substituent in ortho position of the phenyl rings. C.A. Vol. 97(1982) 120105n discloses certain N-arylaklylisoquinolines which may have a hydroxy substituent in the ortho position of a phenyl ring. These compounds have sympatholytic activity and carry aromatic substituents on the nitrogen atom.

It is object of the present invention to provide a novel class of 3,3-diphenylpropylamines having improved anti-cholinergic properties, especially in relation to the effects on these other systems and acute toxicity.

In a first aspect the invention provides novel 3,3-diphenylpropylamines of formula I



I

wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II

II

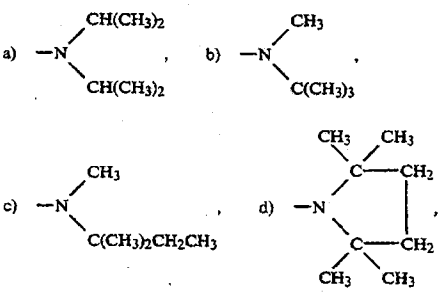
wherein R^5 and R^6 signifky non-aromatic hydrocarbol groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four carbon atoms, especially at least five carbon atoms, and where R^5 and R^6 may form a ring together with the amine nitrogen, said ring preferably having no other hetero atom that the amine nitrogen.

The compounds of formula I can form sales with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

When the novel compounds can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.

A preferred sub-class of compounds according to the invention comprises tertiary amines of formula I, wherein each of R^5 and R^6 independently signifies C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms. R^5 and R^6 may carry one or more hydroxy groups, and they may be joined to form a ring together with the amine nitrogen atom.

Presently preferred tertiary amino-groups X in formula I include the following groups a)–f), each of which may carry one or more hydroxy groups.



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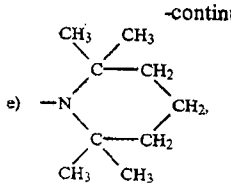
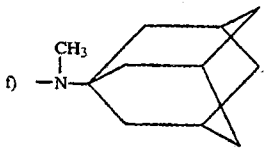
e) 

f) 

The following are examples of presently preferred specific compounds of formula I:

N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine and its (+)-isomer,

N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine,

N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)-propylamine,

N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine,

N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

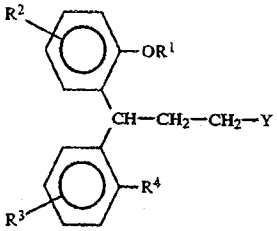
N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,

N,N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine,

N-(3-(2-methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine

In a second aspect the invention provides methods for preparing the compounds of formula I, especially the following methods:

a) reacting a reactively esterified 3,3-diphenylpropanol of formula III



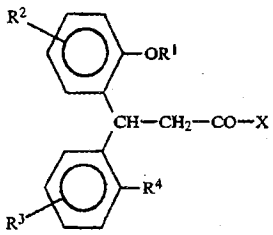
III

wherein R^1–R^4 are as defined above, and any hydroxy groups may be protected such as by methylation or benzylation, and wherein Y is a leaving group, preferably halogen or an alkyl or arylsulphonyloxy group, with an amine of formula IV

IV

wherein X is as defined above, or

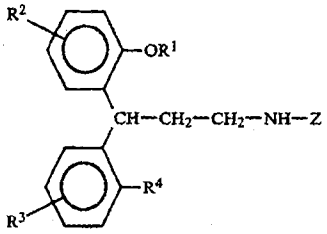
b) reducing a 3,3-diphenylpropionamide of formula V



V

wherein R^1–R^4 and X are as defined above and any hydroxy groups may be protected, preferably using a complex metal hydride,

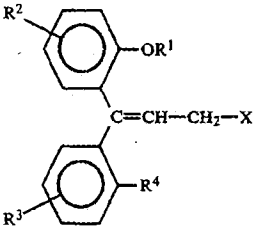
c) N-methylating a secondary 3,3-diphenylpropylamine VI



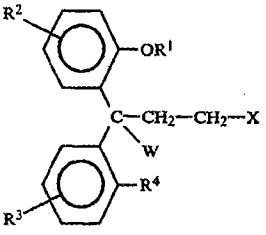
VI

wherein R^1–R^4 are as defined above and any hydroxy groups may be protected, and wherein Z has the same meaning as R^5 and R^6 with the exception of methyl, Z preferably being a hydrocarbyl group comprising at least three carbon atoms, the N-methylation preferably being carried out using formaldehyde or formic acid, or

d) reducing a 3,3-diphenylpropylamine of formula VIIa or VIIb



VIIa



VIIb

wherein R^1–R^4 and X are as defined above and any hydroxy groups may be protected, and W signifies a hydroxy group or a halogen atom, preferably by means of catalytic hydrogenation, and

i) when necessary splitting off hydroxy protecting groups in the compounds obtained, if desired after mono or di-halogenation of one or both of the phenyl rings, and/or

ii) if desired converting obtained bases of formula I into salts thereof with physiologically acceptable acids, or vice versa, and/or

iii) if desired separating an obtained mixture of optical isomers into the individual enantiomers, and/or

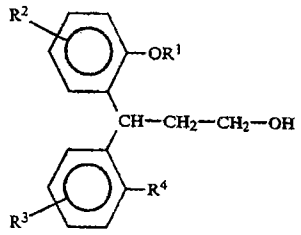
iv) if desired methylating an ortho-hydroxy group in an obtained compound of formula I, wherein R^1 is hydrogen and/or R^4 is hydroxy.

The above general methods can be carried out in a manner known per se and/or in accordance with the working examples described below, with due consideration of the desired amino groups and the substituents on the benzene rings.

The removal of hydroxy protecting groups according to i) above can e.g. be done by treatment with hydrobromic acid, borontribromide or by catalytic hydrogenation.

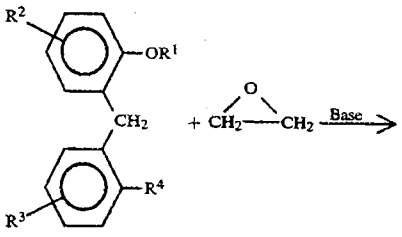
The separation of mixtures of optical isomers, according to ii) above, into the individual enantiomers can e.g. be achieved by fractional crystallization of salts with chiral acids or by chromatographic separation on chiral columns.

Novel compounds of formula VIII



VIII

wherein R^1–R^4 are as defined above, and the corresponding protected compounds (e.g. comprising protected hydroxy groups), are useful as chemical intermediates for the preparation of e.g. the compounds of formula I, and they can be prepared by means of several different methods which are known per se, such as by addition of ethylene oxide (X) to a correspondingly substituted diphenylmethane (IX) in the presence of a suitable base such as sodium amide:



IX X

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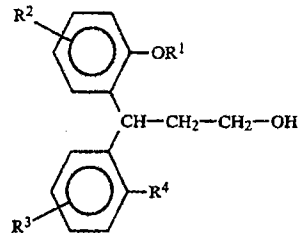


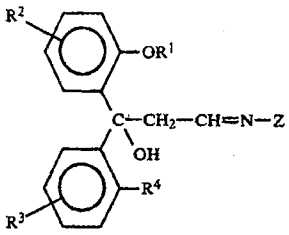
VIII

The compounds VIII can also be prepared by reduction of the corresponding 3,3-diphenylpropionic acids, preferably using complex metal hydrides.

The 3,3-diphenylpropanols VIII can conveniently be converted into the corresponding reactively esterified derivatives III in a manner known per se by displacing the hydroxy groups with e.g. a halogen atom or an alkyl or arylsulphonyloxy group.

The 3,3-diphenylamides of formula V used as starting materials in method b), can e.g. be prepared by reacting the above mentioned 3,3-diphenylpropionic acids with an appropriate amine.

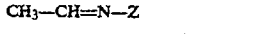
The secondary amines used as starting materials in method c) can conveniently be prepared by reacting a primary amine H_2N-Z (wherein Z is as defined above) with a corresponding reactively esterified 3,3-diphenylpropanol in analogy with method a) above, or by reduction of the corresponding secondary 3,3-diphenylpropionamides in analogy with method b) above. The secondary amines can also be prepared by reduction of unsaturated hydroxyamines XI



XI

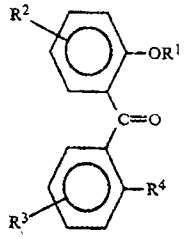
wherein R^1–R^4 and Z are as defined above, either in one step by catalytic hydrogenation, or by reduction to the corresponding saturated hydroxyamine, preferably using a complex metal hydride such as lithium aluminium hydride, followed by removal of the hydroxy group by catalytic reduction. As an alternative, the hydroxy group may first be split off as water, followed by reduction of the formed unsaturated amine.

The unsaturated hydroxy amines XI can conveniently be prepared by the addition of a Schiff base of formula XII



XII

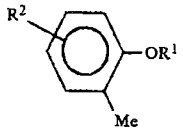
wherein Z is as defined above, to a benzophenone of formula XIII



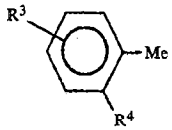
XIII

wherein R^1–R^4 are as defined above, in the presence of a base, preferably a lithium organic base such as lithium diisopropylamide.

Also the starting materials VIIa, VIIb for process d) can be prepared by methods known per se, such as by addition of an organometallic compound XIVa or XIVb

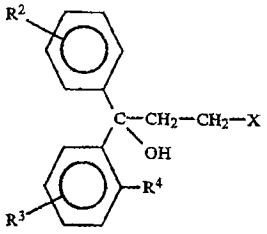


XIVa



XIVb

to a ketoamine XVa or XVb respectively to form a corresponding hydroxy amine XVI



XVI

and, if desired, splitting off water from compound XVI.

In formulae XIVa, XIVb, XVa, XVb, XVI, R^1–R^4 are as defined above, and Me signifies a metal such as magnesium or lithium.

In accordance with the invention the compounds of formula I, in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise the compounds of formula I in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds and compositions according to the invention can be used for treating cholin-mediated disorders such as urinary incontinence. As is well known, the dosage depends on several factors such as the potency of the selected specific compound, the mode of administration, the age and weight of the patient, the severity of the condition to be treated, and the like. The daily dosage may, for example, be from about 0.05 mg to about 4 mg per kilo of body weight, administered in one or more doses, e.g. containing from about 0.05 to about 200 mg each.

The invention will be further illustrated by the following non-limiting examples.

General

^{1}H-NMR spectra were run in $CDCl_3$ using a JEOL PMX60 spectrometer. In some cases, only a limited number of spectral peaks, useful for characterization purposes, are reported.

Reported yields mostly refer to crude material of sufficient purity to be taken to the next stage.

Solvents are abbreviated as follows:
IPE = diisopropyl ether
PET = petroleum ether
Ether = diethyl ether

Amines are abbreviated as follows:
IPA = diisopropyl amine
TBA = tert.butyl amine

Melting points were taken on a Koefler bench.

Temperatures are in °C.

Water is used for the washing steps, unless otherwise stated.

EXAMPLE 1

Preparation of 4-phenyl-3,4-dihydrocoumarins

a) 4-(2-Methoxy-5-methylphenyl)-6-methyl-3,4-dihydrocoumarin (I)

A mixture consisting of 2-methoxy-5-methylcinnamic acid (96.0 g, 0.5 mol), p-cresol (108 g, 1.0 mol), tetraline (200 ml), and conc. sulphuric acid (20 g) was heated slowly to refluxing temperature (145°–150°). After 1½–2 h, the mixture was cooled, taken up in ether, washed with water and sodium carbonate, dried and evaporated, giving 138 g (97%) crude oil. Two recrystallisations from acetone gave white crystals of the desired lactone, m.p. 126°–127°.

$C_{18}H_{18}O_3$ (282.3) requires: C, 76.57; H, 6.43; O, 17.00, Found: C, 76.9; H, 6.44; O, 17.0.

b) 6-Hydroxy-4-phenyl-3,4-dihydrocoumarin (II) was prepared in a similar way in 97% yield from cinnamic acid and hydroquinone. M.p. 138° (IPE-Ether).

$C_{15}H_{12}O_3$ (240.3) requires: C, 74.99; H, 5.04; O, 19.98, Found: C, 75.0; H, 5.00; O, 19.6.

c) 4-(2-Methoxy-4-methylphenyl)-7-methyl-3,4-dihydrocoumarin was obtained in a similar way from 2-methoxy-4-methylcinnamic acid and m-cresol in 58% yield. M.p. 147°–148° (IPE-acetone).

$C_{18}H_{18}O_3$ (282.3) requires: C, 76.57; H, 6.43; O, 17.00, Found: C, 76.4; H, 6.31; O, 17.2.

The above lactone (90 g, 0.32 mol) in methylene chloride (500 ml) was refluxed with BBr_3 (115 g, 0.46 mol) for 24 h, the solution was concentrated, the residue was taken up in ether, the solution was washed with sodium carbonate and water, dried and evaporated,

giving 80 g (93%) of a syrup which crystallized on standing. Crystallization from IPE-PET gave white crystals of

d) 4-(2-hydroxy-4-methylphenyl)-7-methyl-3,4-dihydrocoumarin (III), m.p. 137°.

$C_{17}H_{16}O_3$ (268.3) requires: C, 76.10; H, 6.01; O, 17.89, Found: C, 76.2; H, 6.30; O, 17.0.

e) 8-Hydroxy-4-phenyl-3,4-dihydrocoumarin (IV) was obtained in a similar way from cinnamic acid and catechol in 18% yield. M.p. 136° (IPE).

$C_{15}H_{12}O_3$ (240.2) requires: C, 74.99; H, 5.04; O, 19.98, Found: C, 75.0; H, 5.01; O, 19.9.

f) 4-(2-Methoxyphenyl)-3,4-dihydrocoumarin (V) was obtained in a similar way in 45% yield from methyl 2-methoxycinnamate and phenol. The crude reaction mixture was contaminated with methyl 3-(4-hydroxyphenyl)-3-(2-methoxyphenyl)-propionate. After removal of this by-product with ice-cold NaOH, the title compound was obtained as an oil of sufficient purity to be taken to the next step.

EXAMPLE 2

Preparation of 3,3-diphenylpropionic acid esters

a) Methyl 3-(2-methoxy-4-methylphenyl)-3-phenylpropionate (VI)

7-Methyl-4-phenyl-3,4-dihydrocoumarin (78 g, 0.327 mol) in 150 ml methanol and 150 ml acetone containing methyl iodide (100 g, 0.7 mol) and K_2CO_3 (55 g, 0.4 mol) was refluxed for 24 h, filtered, and the solvent was evaporated. The residue was dissolved in ether, the solution was washed with water, dried and evaporated giving 86 g (92%) of a viscous oil.

NMR: δ 6.6–7.2 (m 8H), 4.9 (t 1H), 3.8 (s 3H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 3H).

b) Methyl 3,3-bis-(2-methoxyphenyl)-propionate (VII) was obtained in the same way in 96% yield from the lactone (V) of Example 1f), m.p. 84°–87° (IPE).

$C_{18}H_{20}O_4$ (300.4) requires: C, 71.98; H, 6.71; O, 21.3, Found: C, 71.4; H, 6.67; O, 21.6.

c) Methyl 3-(2,3-dibenzyloxyphenyl)-3-phenylpropionate (VIII) was obtained in a similar way in quantitative yield from the lactone (IV) of Example 1e) and benzyl chloride in methanol. In addition to K_2CO_3 the reaction mixture also contained some NaI. M.p. 72° (IPE).

$C_{30}H_{28}O_4$ (452.5) requires: C, 79.63; H, 6.24; O, 14.14, Found: C, 79.9; H, 6.15; O, 14.1.

d) Methyl 3-(2-benzyloxyphenyl)-3-phenylpropionate (IX) was obtained in a similar way as a viscous oil in 81% yield from 4-phenyl-3,4-dihydrocoumarin and benzyl chloride.

NMR: δ 7.2 (m 14H), 4.9 (s 2H, t 1H), 3.5 (s 3H), 3.0 (t 2H).

e) Methyl 3-(2-methoxy-5-methylphenyl)-3-phenylpropionate (X) was obtained in a similar way from 6-methyl-4-phenyl-3,4-dihydrocoumarin in 96% yield.

NMR: δ 7.4 (m 8H), 5.0 (t 1H), 3.9 (s 3H), 3.7 (s 3H), 3.2 (d 2H), 2.4 (s 3H).

f) Methyl 3,3-bis-(2-methoxy-5-methylphenyl)propionate (XI) was obtained in a similar way in quantitative yield from the lactone (I) of Example 1a) and methyl iodide.

NMR: δ 6.6–7.1 (m 6H), 5.1 (t 1H), 3.7 (s 6H), 3.5 (s 3H), 3.0 (d 2H), 2.2 (s 6H).

g) Methyl 3-(2,5-dibenzyloxyphenyl)-3-phenylpropionate (XII) was obtained in a similar way in 90% yield from the lactone (II) of Example 1b) and benzyl chloride.

NMR: δ 6.8–7.4 (m 18H), 5.0 (s 4H, t 1H), 3.7 (s 3H), 3.1 (d 2H).

h) Methyl 3,3-bis-(2-benzyloxy-4-methylphenyl)propionate (XIII) was obtained in a similar way in 95% yield from the lactone (III) of Example 1d) and benzyl chloride. By GLC the product is homogenous, and by MS it has the correct M.W.

i) Ethyl 3-(2,4-dimethoxyphenyl)-3-phenylpropionate (XIV)

A mixture of ethyl cinnamate (88 g, 0.5 mol), dimethyl resorcinol (276 g, 2.0 mol) and conc. sulphuric acid (50 g) was stirred on a boiling water-bath for 2 h, whereafter all the volatile material was distilled off in vacuum. The residual oil was dissolved in ether, the solution was washed with sodium carbonate, dried, and evaporated giving 101 g (64%) of the title ester in the form of a viscous oil.

NMR: δ 6.4–7.2 (m 8H), 4.9 (t 1H), 4.0 (q 2H), 3.7 (s 6H), 3.0 (d 2H), 1.1 (t 3H).

j) Methyl 3,3-bis-(2,4-dimethoxyphenyl)propionate (XV) was obtained in a similar way from methyl 2,4-dimethoxycinnamate and dimethyl resorcinol. The product thus obtained contained about 23% of dimethyl resorcinol. It was taken to the next step without further purification.

k) Methyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropionate

6-Chloro-4-phenyl-3,4-dihydrocoumarin (435 g, 1.68 mol. Preparation: T. Manimaran & V. T. Ramakrishnan, Ind. J. Chem. B 18 (1979) 328) is added to a hot solution of sodium hydroxide (140 g, 3.5 mol) in water (500 ml). The solution is chilled to 25° C. and dimethyl sulphate (442 g, 3.5 mol) is added dropwise during 1 h with stirring and cooling at 25°–35° C. The mixture is stirred for an additional 2 h whereupon a solution of 100 g of sodium hydroxide in 500 ml of water is added and the mixture is stirred until a clear solution is obtained. An excess of concentrated hydrochloric acid is added to precipitate the methoxy acid, which separates as an oil which slowly crystallizes. It is filtered off, washed with water and dried. Crystallization from 2-propanol gives colourless crystals of 3-(5-chloro-2-methoxyphenyl)-3-phenyl propionic acid, m.p. 144° C. Yield 455 g.

The above acid (291 g, 1.0 mol) in 1 liter methanol containing 50 g concentrated sulphuric acid was refluxed for 8 h. The solvent was distilled off, the residue was taken up in ether, washed with water and sodium carbonat solution, dried and evaporated giving 300 g (100%) crude oil. Recrystallisation from IPE gave white crystals of the title compound, m.p. 65°–66°.

$C_{17}H_{17}ClO_3$ (304,8) requires: C, 67.0; H, 5.62; Cl, 11.63, Found: C, 68.1; H, 5.82; Cl, 11.7.

EXAMPLE 3

Preparation of 3,3-diphenylpropanols

a) 3-(2-Methoxy-4-methylphenyl)-3-phenylpropanol (XVI)

The ester (VI) of Example 2a) (84 g, 0.295 mol) in 150 ml dry ether was added dropwise to a suspension of $LiAlH_4$ (11.3 g, 0.295 mol) in 300 ml dry ether. The mixture was stirred overnight, then decomposed by the careful addition first of 11 g of water, then of 15% NaOH until a white granular precipitate was formed. The mixture was filtered, the filtrate was washed with

water, dried, and evaporated giving 71 g (91%) of an oil which crystallized on standing. Recrystallization from IPE-PET gave white crystals, m.p. 83°.

$C_{17}H_{20}O_2$ (256.4) requires: C, 79.65; H, 7.88; O, 12.48, Found: C, 79.4; H, 7.89; O, 12.7.

b) 3,3-Bis-(2-methoxyphenyl)propanol (XVII) was obtained in a similar manner in quantitative yield as a viscous oil from the ester (VII) of Example 2b).

c) 3-(2,3-Dibenzyloxyphenyl)-3-phenylpropanol (XVIII) was obtained in a similar way as a viscous oil in 96% yield from the ester (VII) of Example 2c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropanol (XIX) was obtained in a similar was as an oil in 78% yield from the ester (IX) of Example 2d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropanol (XX) was obtained in a similar way as an oil in quantitative yield from the ester (X) of Example 2e).

NMR: δ 6.8–7.4 (m 7H), 4.7 (t 1H), 3.8 (s 3H), 3.7 (m 2H), 2.3 (s 3H), 2.0–2.3 (m 2H).

f) 3,3-Bis-(2-methoxy-5-methylphenyl)propanol (XXI) was obtained in a similar way in 98% yield from the ester (XI) of Example 2f). M.p. 89° (IPE).

$C_{19}H_{24}O_3$ (300.4) requires: C, 75.97; H, 8.05; O, 15.98, Found: C, 75.9; H, 8.02; O, 16.1.

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropanol (XXII) was obtained in a similar way in 88% yield from the ester (XII) of Example 2g). M.p. 78° (IPE).

$C_{29}H_{28}O_3$ (424.5) requires: C, 82.05; H, 6.65; O, 11.31, Found: C, 82.0; H, 6.62; O, 11.2.

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)propanol (XXIII) was obtained in a similar way as an oil in 93% yield from the ester (XIII) of Example 2h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropanol (XXIV) was obtained as a golden oil in 92% yield from the ester (XIV) of Example 2i).

NMR: δ 6.5–7.2 (m 8H), 4.5 (t 1H), 3.8 (s 6H), 3.6 (m 2H), 2.0–2.6 (m 3H).

j) 3,3-Bis-(2,4-dimethoxyphenyl)propanol (XXV) was obtained in a similar way from the impure ester (XV) of Example 2j). By NMR, the product contains about 20% of dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)propanol (XXVI)

A Grignard reagent was prepared in the usual manner from o-bromoanisole (93.5 g, 0.5 mol) and magnesium (12 g, 0.5 mol) in 100 ml dry ether. A solution of p-fluorobenzaldehyde (62 g, 0.5 mol) in 100 ml ether was added dropwise to this solution. After about 1 h, the mixture was decomposed with NH_4Cl and worked up, giving 100.6 g (87%) of 4-fluoro-2'-methoxy-diphenylmethanol. Recrystallization from IPE-PET gave white crystals, m.p. 88°.

$C_{14}H_{13}FO_2$ (232.3) requires: C, 72.40; H, 5.64, Found: C, 72.9; H, 5.75.

The obtained carbinol (46.2 g, 0.2 mol) in 600 ml ethanol was hydrogenated in the presence of 4 g of 5% Pd/C catalyst. After about 5–6 h, the reaction was complete and the mixture was worked up giving 40 g (93%) of 4-fluoro-2'-methoxy-diphenylmethane as a clear oil.

NMR: 6.8–7.2 (m 8H), 4.0 (s 2H), 3.8 (s 3H).

The obtained methane derivative (71 g, 0.33 mol) in 100 ml ether was added to a solution of $NaNH_2$ prepared in situ from sodium (8.5 g, 0.37 mol) in about 300 ml of NH_3. After about 1 h, a solution of ethylene oxide (17.5 g, 0.395 mol) in 75 ml ether was added dropwise. The mixture was stirred for 2 h, and most of the ammonia was then removed with a stream of air. Solid NH_4Cl was then added, followed by the addition of water. The organic phase was separated, washed with water and 2N HCl, dried and evaporated, giving 81.5 g (95%) of the title compound. M.p. 61° (IPE-PET).

$C_{16}H_{17}FO_2$ (260.3) requires: C, 73.82; H, 6.58, Found: C, 74.1; H, 6.77.

l) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropanol

The ester from Example 2k) (91.5 g, 0.3 mol) in 500 ml dry ether was added dropwise under nitrogen to $LiAlH_4$ (11.4 g, 0.3 mol) in 200 ml dry ether. The mixture was stirred at room temperature overnight, then decomposed with 11 g water and 11 g 15% NaOH solution. Work up gave 72.5 g (87.5%) colourless oil. Recrystallization from IPE gave white crystals of the title compound, m.p. 80°.

$C_{16}H_{17}ClO_2$ (276.8) requires: C, 69.43; H, 6.19; Cl, 12.81, Found: C, 70.1; H, 6.44; Cl, 12.9.

EXAMPLE 4

Preparation of 3,3-diphenylpropyl-p-toluene sulphonates

a) 3,3-Bis-(2-methoxyphenyl)propyl-p-toluene sulphonate (XXVII)

The propanol (XVII) of Example 3b) (35 g, 0.128 mol) in 100 ml chloroform containing 30 ml pyridine was cooled to about −10° and then treated with p-toluene sulphonyl chloride (29 g, 0.15 mol). After standing in the cooler (about +5° C.) overnight, the mixture was poured into ice-water, the organic phase was washed with water and cold 2N HCl, dried, and the solvent was distilled off at <50° C., giving a crude oil in quantitative yield. Recrystallization from IPE gave white crystals of low and indefinite m.p.

$C_{24}H_{26}O_5S$ (426.5) requires: C, 67.58; H, 6.14; S, 7.52, Found: C, 66.8; H, 6.22; S, 7.76.

b) 3(2-Methoxy-4-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXI) was obtained in quantitative yield from the propanol (XVI) of Example 3a).

c) 3-(2,3-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXVIII) was obtained in a similar way as a thick oil in 88% yield from the propanol (XVIII) of Example 3c).

d) 3-(2-Benzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXIX) was obtained in i similar way in 98% yield from the propanol (XIX) of Example 3d).

e) 3-(2-Methoxy-5-methylphenyl)-3-phenylpropyl-p-toluene sulphonate (XXX) was obtained in quantitative yield from the propanol (XX) of Example 3e). M.p. 64° (IPE-PET).

$C_{23}H_{24}O_4S$ (396.5) requires: C, 69.67; H, 6.10; S, 8.09, Found: C, 69.8; H, 6.20; S, 7.85.

f) 3,3-Bis-(2-methoxy-5-methylphenyl)-propyl-p-toluene sulphonate (XXXII) was obtained in quantitative yield from the propanol (XXI) of Example 3f). M.p. 117° (acetone-PET).

$C_{26}H_{30}O_5S$ (454.5) requires: C, 68.7; H, 6.65; S, 7.05, Found: C, 68.8; H, 6.66; S, 7.11.

g) 3-(2,5-Dibenzyloxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXIII) was obtained in a similar manner in quantitative yield from the propanol (XXII) of Example 3g).

h) 3,3-Bis-(2-benzyloxy-4-methylphenyl)-propyl-p-toluene sulphonate (XXXIV) was obtained in a similar way in 86% yield from the propanol (XXIII) of Example 3h).

i) 3-(2,4-Dimethoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XXXV) was in the same way obtained in 96% yield from the propanol (XXIV) of Example 3i).

j) 3,3-Bis-(2,4-dimethoxyphenyl)-propyl-p-toluene sulphonate (XXXVI) was obtained in the same manner from the propanol (XXV) of Example 3j). The product was contaminated with dimethyl resorcinol.

k) 3-(4-Fluorphenyl)-3-(2-methoxyphenyl)-propyl-p-toluene sulphonate (XXXVII) was obtained in a similar way in 88% yield from the propanol (XXVI) of Example 3k). M.p. 67° (IPE).

$C_{23}H_{23}FO_4S$ (414.5) requires: C, 66.65; H, 5.59; S, 7.74, Found: C, 67.1; H, 5.69; S, 7.78.

l) 3-(2-Methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate (XLVIII)

A mixture of anisole (1080 g, 10 mol), benzyl alcohol (216 g, 2 mol) and p-toluene sulphonic acid (40 g) was refluxed for 2 h in an apparatus equipped with a water separator. Excess of anisole was then distilled off, the oily residue was dissolved in ether, washed with water and sodium carbonate, dried and fractionated, giving 304 g (77%) of a pale yellow oil, b.p. 115°–118°/0.4 Torr. By NMR, it is a 1:1 mixture of o-methoxy and p-methoxy diphenyl methane. This material was converted to a mixture of the corresponding propanols by reaction with ethylene oxide, as in the preparation of the propanol (XXVI) of Example 3k). This mixture of propanols was then converted as described above to a mixture of p-toluene sulphonates from which the title-compound could be isolated in 35% yield after two recrystallizations from IPE. M.p. 108°.

$C_{23}H_{24}O_4S$ (396.5) requires: C, 69.67; H, 6.10; S, 8.09, Found: C, 69.3; H, 6.00; S, 8.17.

m) 3-(5-Chloro-2-methoxyphenyl)-3-phenylpropyl-p-toluene sulphonate

The alcohol from Example 3l) (66 g, 0.24 mol) in 300 ml chloroform containing 75 ml pyridine was treated portionswise in the cold with p-toluene-sulphonyl chloride (55 g, 0.29 mol). The mixture was kept at 5° C. for 18 h, solvent was evaporated under vacuum at <50°, the residue was taken up in ether, washed with water and 2N HCl, dried and evaporated giving 100 g (97%) of a straw-yellow syrup. Recrystallization from IPE gave the title compound, m.p. 89°–90°.

$C_{23}H_{23}ClO_4S$ (430.96) requires: C, 64.10; H, 5.38; S, 7.44; Cl, 8.23, Found: C, 64.4; H, 5.45; S, 7.04; Cl, 8.17.

EXAMPLE 5

Preparation of tertiary 3,3-diphenylpropylamines

a) N,N-Diisopropyl-3,3-bis-(2-methoxyphenyl)-propylamine (XXXVIII), hydrogen oxalate

The tosylate (XXVII) of Example 4a) (42.6 g, 0.1 mol) in 100 ml acetonitrile and 100 g (1.0 mol) diisopropylamine was heated in a pressure bottle at 80° for 4–6 days. Volatile material was then evaporated, the residue was treated with excess of 2N NaOH and extracted with ether. The extract was washed with water and extracted with 2N HCl. This extract was washed with ether, basified, extracted with ether, washed with water, dried, decoloured, filtered, and evaporated, giving 24.0 g (68%) of a crude oil. This oil was converted to the oxalic acid salt by treating an acetone solution of the base with one equivalent of oxalic acid in acetone. M.p. 160°–161° (acetone).

$C_{25}H_{35}NO_6$ (445.6) requires: C, 67.39; H, 7.92; N, 3.14; O, 21.55, Found: C, 67.2; H, 8.22; N, 2.94; O, 21.9.

b) N,N-Diisopropyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (XXXIX)

The free base was obtained in the same way in 75% yield from the tosylate (XXVIII) of Example 4c).

NMR: 6.9–7.2 (m 18H), 5.0 (s 4H), 0.9 (d 12H).

c) N,N-Diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (XL), hydrogenfumarate

The free base was obtained in 69% yield from the tosylate (XXX) of Example 4e). It was converted to the fumaric acid salt in the usual manner. M.p. 176° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires: C, 71.17; H, 8.20; N, 3.07; O, 17.6, Found: C, 71.3; H, 8.27; N, 3.04; O, 17.9.

d) N,N-Diisopropyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (XLI), hydrogenfumarate

The free base was obtained in 25% yield from the tosylate (XXXI) of Example 4b). The fumaric acid salt had m.p. 147°–148° (acetone).

$C_{27}H_{37}NO_5$ (455.7) requires: C, 71.17; H, 8.20; N, 3.07; O, 17.6, Found: C, 71.3; H, 8.14; N, 3.00; O, 17.6.

e) N,N-Diisopropyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (XLII), hydrochloride

The free base was obtained in 78% yield from the tosylate (XXXII) of Example 4f). It was converted to the hydrochloride with ethereal HCl in the ususal manner. M.p. 163°–164° (acetone-ether).

$C_{25}H_{38}NO_2Cl$ (420.1) requires: C, 71.49; H, 9.12; N, 3.33; O, 7.61; Cl, 8.44, Found: C, 71.6; H, 9.08; N, 3.27; O, 7.93; Cl, 8.36.

f) N,N-Diisopropyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (XLIII)

The free base was obtained in 70% yield from the tosylate (XXXIII) of Example 4g).

NMR: δ 6.6–7.2 (m 18H), 5.0 (s 4H), 4.5 (t 1H), 1.0 (d 12H).

g) N,N-Diisopropyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propylamine (XLIV)

The free base was obtained in 62% yield from the tosylate (XXXIV) of Example 4h).

NMR: δ 6.8–7.2 (m 16H), 4.8 (s 4H, t 1H), 0.9 (d 12H).

h) N,N-Diisopropyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (XLV)

The free base was obtained in 56% yield from the tosylate (XXXV) of Example 4i).

NMR: 6.5–7.3 (m 8H), 4.4 (t 1H), 3.8 (s 6H), 1.0 (d 12H).

i) N,N-Diisopropyl-3,3-bis-(2,4-dimethoxyphenyl)-propylamine (XLVI)

The free base was obtained in 34% yield from the tosylate (XXXVI) of Example 4j).

NMR: δ 6.5–7.3 (m 6H), 4.6 (t 1H), 3.9 (s 12H), 1.0 (d 12H).

j) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)propylamine XLVII)

The free base was obtained in 71% yield from the tosylate (XXXVII) of Example 4k).

k) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine (XLIX), hydrogen fumarate

The free base was obtained in 86% yield from the tosylate (XLVIII) of Example 4l) and was converted to the fumaric acid salt in the usual way. M.p. 134°–136° (acetone-IPE) or 163°–164° (methanol).

$C_{26}H_{36}NO_5$ (441.6) requires: C, 70.72; H, 7.99; N, 3.28; O, 18.12, Found: C, 70.8; H, 7.93; N, 3.28; O, 18.1.

l) N-(3-(2-Methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine (LXIV)

This compound was obtained in the same way in 54% yield from the tosylate (XLVIII) of Example 4l) and 2,2,6,6-tetramethylpiperidine. M.p. 100° (IPE).

$C_{25}H_{35}NO$ (365.6) requires: C, 82.14; H, 9.65; N, 3.83, Found: C, 82.0; H, 9.62; N, 3.57.

m) N,N-diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) was heated for 4 days at 80° with diisopropylamine (50 g, 0.5 mol) in 100 ml acetonitrile, giving 23 g (64%) of crude title compound. By GC, it is at least 93% pure.

n) N-(3-(2-Benzyloxyphenyl)-3-phenylpropyl)-2,2,5,5-tetramethylpyrrolidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2,2,5,5-tetramethylpyrrolidine. It was obtained as a sticky oil, which was converted to the hydroxy analogue without further purification (Example 9ab)).

o) N-(3-(2-Benzyloxyphenyl)-3-phenylpropyl)-4-hydroxy-2,2,6,6-tetramethylpiperidine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 4-hydroxy-2,2,6,6-tetramethylpiperidine, and it was obtained as a sticky oil which was converted to the hydroxy compound without further purification (Example 9ac)).

p) N-(2-Hydroxy-1,1-dimethylethyl)-3-(2-benxyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the tosylate (XXIX) of Example 4d) and 2-amino-2-methylpropanol. The solid product was crystallized from diisopropyl ether and melted at 103° C. It was used as start material in (Example 7p).

$C_{26}H_{31}NO_2$ (389.5) requires: C, 80.17; H, 8.02; N, 3.60; O, 8.22, Found; C, 80.0; H, 8.09; N, 3.69; O, 8.51.

q) N-(1-Adamantyl)-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the toyslate (XXIX) of Example 4d) and 1-aminoadamantane. It was used as start material in Example 7q). The hydrochloridesemihydrate was prepared in acetonitrile and melted at 225° C.

$C_{32}H_{37}NO.HCl.\frac{1}{2}\ H_2O$ (497.1) requires: C, 77.31; H, 7.91; N, 2.82; O, 4.83; Cl, 7.13, Found: C, 77.3; H, 8.23; N, 2.65; O, 5.04; Cl, 7.14.

EXAMPLE 6

Preparation of secondary 3,3-diphenylpropylamines

a) N-tert.Butyl-3,3-bis-(2-methoxyphenyl)propylamine (L), hydrogen oxalate

The tosylate (XXVII) of Example 4a) was heated with a large excess of tert.butylamine as described in Example 5, giving the free base in 78% yield, which was converted to the oxalic acid salt in the usual manner. M.p. 135°-136° (acetone-ether).

$C_{23}H_{31}NO_6$ (417.5) requires: C, 66.17; H, 7.48; N, 3.36; O, 22.99, Found: C, 65.6; H, 7.31N, 3.36; O, 23.4.

b) N-ter.Butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (LI), hydrochloride

The free base was obtained as above in 78% yield from the tosylate (XXVIII) of Example 4c). The HCl salt had m.p. 184°-185° (acetone-methanol-IPE).

$C_{33}H_{38}NO_2Cl$ (516.1) requires: C, 76.79; H, 7.42; N, 2.71; O, 6.20; Cl, 6.87, Found: C, 76.3; H, 7.30; N, 2.72; O, 6.42; Cl, 6.81.

c) N-tert.Butyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine (LII), hydrogen oxalate

The free base was obtained in 84% yield from the tosylate (XXIX) of Example 4d). The oxalic acid salt had m.p. 198° (acetone-ether).

$C_{28}H_{33}NO_5$ (463.6) requires: C, 72.54; H, 7.18; N, 3.02, Found: C, 71.8; H, 7.13; N, 2.95.

d) N-tert.Butyl-3-(2-methoxy-5-methyplenyl)-3-phenylpropylamine (LIII), hydrochloride

The free base was obtained in 90% yield from the tosylate (XXX) of Example 4e). When treated with ethereal HCl, it gave a somewhat hygroscopic salt which seems to be associated with ¼ mol water. Mp. 171° ethanol-ether).

$C_{21}H_{29}NO.HCl.\frac{1}{4}\ H_2O$ (352.5) (requires): C, 71.55; H, 8.74; N, 3.97; O, 5.67; Cl, 10.06, Found: C, 71.8; H, 8.72; N, 4.05; O, 5.57; Cl, 10.1.

e) N-ter.Butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (LIV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXI) of Example 4b). The HCl-salt had m.p. 138°-149° (methanol-isopropanol). It was associated with ⅜ mol of water.

$C_{21}H_{30}NOCl.\frac{3}{8}\ H_2O$ (361.5) requires: C, 69.77; H, 8.80; N, 3.88; Cl, 9.81, Found: C, 69.8; H, 8.76; N, 3.93; Cl, 9.75.

f) N-ter.Butyl-3,3-bis-(2-methoxy-5-methylphenyl)-propylamine (LV), hydrochloride

The free base was obtained in quantitative yield from the tosylate (XXXII) of Example 4f). The HCl-salt had m.p. 242° (acetone).

$C_{23}H_{34}NOCl$ (392.0) requires: C, 70.47; H, 8.74; N, 3.57; Cl, 9.05, Found: C, 70.2; H, 8.81; N, 3.46; Cl, 8.99.

g) N-tert.Butyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (LVI), hydrochloride

The free base was obtained in 85% yield from the tosylate (XXXIII) of Example 4g). The HCl salt had m.p. 188° (ethanol-ether).

$C_{33}H_{38}NO_2Cl$ (516.1) requires: C, 76.79; H, 7.42; N, 2.71; O, 6.20; Cl, 6.87, Found: C, 77.2; H, 7.50; N, 2.64; O, 6.53; Cl, 6.85.

h) N-tert.Butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)-propylamine (LVII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXIV) of Example 4h). The HCL-salt had m.p. 210° (acetone-ether).

$C_{35}H_{42}NO_2Cl$ (544.2) requires: C, 77.25; H, 7.78; N, 2.57; O, 5.89; Cl, 6.52, Found: C, 77.6; H, 7.82; N, 2.35; O, 6.08; Cl, 6.55.

i) N-tert.Butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (LVIII), hydrochloride

The free base was obtained in 84% yield from the tosylate (XXXV) of Example 4i). The HCl-salt had m.p. 196° (acetone-ethanol-ether).

$C_{21}H_{30}NO_2Cl$ (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.3; H, 8.44; N, 3.80; O, 8.89; Cl, 9.81.

j) N-tert.Butyl-3,3-bis-(2,4-dimethoxyphenyl)-propylamine (LIX), hydrochloride

The free base was obtained in 60% yield from the tosylate (XXXVI) of Example 4j). The HCl-salt had m.p. 251° (methanol-acetone).

$C_{23}H_{34}NO_4Cl$ (424.0) requires: C, 65.15; H, 8.08; N, 3.30; O, 15.09; Cl, 8.36, Found: C, 64.5; H, 8.06; N, 3.57; O, 15.3; Cl, 8.67.

k) N-tert.Butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)-propylamine (LX), hydrochloride

The free base was obtained in 89% yield from the tosylate (XXXVII) of Example 4k). The HCl-salt had m.p. 194° (ethanol-acetone).

$C_{20}H_{27}NOFCl$ (351.9) requires: C, 68.26; H, 7.73; N, 3.98; Cl, 10.08, Found: C, 68.9; H, 7.97; N, 4.01; Cl, 9.69.

l) N-tert.Butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXI), hydrochloride

The free base was obtained in 88% yield from the tosylate (XLVIII) of Example 4l). The HCl-salt had m.p. 205°.

$C_{20}H_{28}NOCl$ (333.9) requires: C, 71.94; H, 8.45; N, 4.20; O, 4.79, Found: C, 71.9; H, 8.44; N, 4.67; O, 4.79.

m) N-(1,1-Dimethylpropyl)-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXII), hydrochloride

The free base was obtained in 95% yield from the tosylate (XXX) of Example 4e) and tert. amylamine. The HCl-salt had m.p. 188°–189° (ethanol-acetone).

$C_{22}H_{32}NOCl$ (362.0) requires: C, 73.00; H, 8.91; N, 3.87; O, 4.42; Cl, 9.80, Found: C, 73.4; H, 8.98; N, 3.83; O, 4.61; Cl, 9.51.

n) N-(1,1-Dimethylpropyl)-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXIII), hydrochloride

The free base was obtained in 94% yield from the tosylate (XXXII) of Example 4f) and tert.amylamine. The HCl-salt had m.p. 210° (ethanol-acetone).

$C_{24}H_{36}NO_2Cl$ (406.0) requires: C, 71.00; H, 8.94; N, 3.45; O, 7.88; Cl, 8.73, Found: C, 71.1; H, 9.01; N, 3.60; O, 7.92; Cl, 8.73.

o) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The tosylate from Example 4m) (43.1 g, 0.1 mol) in 100 ml acetonitrile was treated with tert.butylamine (37 g, 0.5 mol) and the mixture was heated in a pressure bottle at 80° for 4 days. The usual work-up afforded 32 g (100%) crude title compound. The base in ether-acetone was treated with ethereal HCl giving the hydrochloride salt, m.p. 216°–218°.

$C_{20}H_{26}ClNO.HCl$ (368.36) requires: C, 65.21; H, 7.39; N, 3.80; Cl, 19.25, Found: C, 65.1; H, 7.39; N, 3.90; Cl, 18.7.

EXAMPLE 7

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

a) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-phenylpropylamine (LXV), hydrochloride

A mixture of the secondary amine (LXI) of Example 6l) (29.7 g, 0.1 mol), formic acid (13.8 g, 0.3 mol), and 37% formaldehyde solution (12.5 g, 0.12 mol) was refluxed for 18–24 h. The mixture was then cooled, basified with NaOH, and extracted with ether. The extract was washed with water, dried and evaporated, giving 29.3 g (94%) of a crude oil. The HCl-salt was prepared from ethereal HCl in the usual way, m.p. 199°.

$C_{21}H_{30}NOCl$ (347.9) requires: C, 72.49; H, 8.69; N, 4.03; Cl, 10.19, Found: C, 71.9; H, 8.79; N, 4.23; Cl, 10.1.

b) N-Methyl-N-tert.butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXVI), hydrochloride

The free base was obtained in the same way in 89% yield from the amine (LIII) of Example 6d). The HCl-salt had m.p. 161° (acetone).

$C_{22}H_{32}NOCl$ (362.0) requires: C, 73.00; H, 8.91; N, 3.87; O, 4.42; Cl, 9.08, Found: C, 73.0; H, 8.96; N, 3.94; O, 4.59; Cl, 9.77.

c) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxyphenyl)-propylamine (LXVII), hydrochloride

The free base was obtained in 96% yield from the amine (L) of Example 6a). The HCl-salt had m.p. 187°–190° (acetone-ether).

$C_{22}H_{33}NOCl$ (378.0) requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, , 69.9; H, 8.56; N, 3.53; O, 8.93; Cl, 8.92.

d) N-Methyl-N-tert.butyl-3-(2-methoxy-4-methylphenyl)-3-phenylpropylamine (LXVIII)

The free base was obtained in 96% yield from the amine (LIV) of Example 6e). M.p. 64° (IPE).

$C_{22}H_{31}NO$ (325.5) requires: C, 81.17; H, 9.60; N, 4.30; O, 4.92, Found: C, 81.0; H, 9.83; N, 4.15; O, 5.03.

e) N-Methyl-N-tert.butyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXIX)

The free base was obtained in 97% yield from the amine (LV) of Example 6f). M.p. 95° (IPE).

$C_{24}H_{35}NO_2$ (370.0) requires: C, 78.00; H, 9.55; N, 3.79; O, 8.66, Found: C, 78.1; H, 9.57; N, 3.70; O, 8.80.

f) N-Methyl-N-tert.butyl-3-(4-fluorophenyl)-3-(2-methoxyphenyl)propylamine (LXX), hydrochloride

The free base was obtained in 82% yield from the amine (LX) of Example 6k). The HCl-salt had m.p. 218° (ethanol-acetone).

$C_{21}H_{29}NOClF$ (365.9) requires: C, 68.93; H, 7.99; N, 3.83; Cl, 9.69, Found: C, 69.0; H, 7.97; N, 3.95; Cl, 9.60.

g) N-(1,1-Dimethylpropyl)-N-methyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine (LXXI), hydrochloride

The free base was obtained in 98% yield from the amine (LXII) of Example 6m). The HCl-salt had m.p. 176°–177° (acetone).

$C_{23}H_{34}NOCl$ (376.0) requires: C, 73.47; H, 9.11; N, 3.73; Cl, 9.43, Found: C, 73.4; H, 9.15; N, 3.73; Cl, 9.41.

h) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-methoxy-5-methylphenyl)propylamine (LXXII), hydrochloride

The free base was obtained in 89% yield from the amine (LXIII) of Example 6n). The HCl-salt had m.p. 147° (acetone-ether).

$C_{25}H_{37}NO_2Cl$ (420.1) requires: C, 71.49; H, 9.12; N, 3.34; O, 7.62; Cl, 8.44, Found: C, 70.8; H, 9.20; N, 3.63; O, 7.74; Cl, 8.42.

i) N-Methyl-N-tert.butyl-3-(2,4-dimethoxyphenyl)-3-phenylpropylamine (LXXIII)

This compound was obtained as an oil in quantitative yield from the amine (LVIII) of Example 6i).

NMR: 6.5–7.3 (m 8H), 4.3 (t 1H), 3.8 (s 6H), 2.3 (s 3H), 1.0 (s 9H).

j) N-Methyl-N-tert.butyl-3-(2,5-dibenzyloxyphenyl)-3-phenylpropylamine (LXXIV)

This was obtained as an oil in 95% yield from the amine (LVI) of Example 6g).

k) N-Methyl-N-tert.butyl-3,3-bis-(2-benzyloxy-4-methylphenyl)propylamine (LXXV), hydrochloride

The free base was obtained in 92% yield from the amine (LVII) of Example 6k). The HCl-salt had m.p. 170°–171° (acetone-ether).

$C_{36}H_{44}NO_2Cl$ (558.2) requires: C, 77.46; H, 7.95; N, 2.51; O, 5.73; Cl, 6.35, Found: C, 77.6; H, 7.86; N, 2.42; O, 5.89; Cl, 6.31.

l) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dimethoxyphenyl)propylamine (LXXVI), hydrochloride

The free base was obtained in 96% yield from the amine (LIX) of Example 6j). The HCl-salt had m.p. 180°–190° and seems to be associated with ¼ mol of water.

$C_{24}H_{36}NO_4Cl$ ¼ H_2O (447.0) requires: C, 64.48; H, 8.34; N, 3.13; O, 16.11; Cl, 7.93, Found: C, 64.5; H, 8.27; N, 3.02; O, 16.2; Cl, 8.19.

m) N-Methyl-N-tert.butyl-3-(2,3-dibenzyloxyphenyl)-3-phenylpropylamine (LXXVII)

This was obtained as an oil in 98% yield from the amine (LI) of Example 6b).

NMR: δ 6.9–7.3 (m 18H), 2.1 (s 3H), 1.0 (s 9H).

n) N-Methyl-N-tert.butyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine (LXXVIII)

This was obtained as an oil in 97% yield from the amine (LII) of Example 6c).

NMR: 6.9–7.3 (m 14H), 5.0 (s 4H), 4.5 (t 1H), 2.2 (s, 3H), 0.9 (s, 9H).

o) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-phenylpropylamine

The secondary amine from Example 6o) (25.3 g, 0.076 mol) was refluxed for 18 h with formic acid (9.2 g, 0.2 mol) and 35% formaldehyde solution (8.5 g, 0.1 mol). Work-up gave 25.6 g, (97.5%) crude base. This was dissolved in acetone and treated with an equimolar quantity of oxalic acid in acetone giving beige crystals of the title compound, hydrogen oxalate, m.p. 165°.

$C_{21}H_{28}ClNO.C_2H_2O_4$ (436.0) requires: C, 63.37; H, 6.94; N, 3.21; Cl, 8.13 , Found: C, 62.7; H, 6.83; N, 3.10; Cl, 7.97.

p) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5p). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ad).

q) N-1-Adamantyl-N-methyl-3-(2-benzyloxyphenyl)-3-phenylpropylamine

This compound was similarly prepared from the compound of Example 5q). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 9ae) without further purification.

EXAMPLE 8

Preparation from olefinic precursors

a) N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-hydroxy-3-phenylpropylamine (LXXIX)

A solution of diisopropylamine (10.1 g, 0.1 mol) in dry ether (100 ml) was cooled to −10°. A solution of butyl lithium in hexane (65 ml, 0.1 mol) was added, and the mixture was stirred at −10° for 20 min. A solution of N-ethylidene-tert.butylamine (10 g, 0.1 mol) in dry ether (100 ml) was added and the solution was stirred at 0° for 20 min. After cooling to −30° a solution of 2,6-dimethoxybenzophenone (24.1 g, 0.1 mol) in dry ether (100 ml), containing 30 ml THF, was added. The mixture was then stirred at ambient temperature for 20 h and hydrolized with water. The organic phase was washed with water, dried and evaporated, giving 32 g (94%) of N-(3-(2,6-dimethoxyphenyl)-3-hydroxy-3phenylpropylidene)tert.butylamine as an oil.

This oil was dissolved in absolute ethanol (250 ml), the solution was cooled to −5°, and $NaBH_4$ (5.7 g, 0.15 mol) was added portionwise. The mixture was stirred at 0° for ½ h, then at ambient temperature for 3 h. Most of the solvent was distilled off in vacuum, the residue was treated with water, extracted with ether, washed with water, and extracted with 2N HCl. The extract was washed with ether, basified with NaOH, extracted with ether, dried and evaporated, giving 30 g of the title amine.

The HCl-salt had m.p. 203°–204° (acetone-ether) and seems to be associated with ¼ mol of water.

$C_{21}H_{29}NO_3.HCl.¼\ H_2O$ (384.5) requires: C, 65.60; H, 8.01; N, 3.64; O, 13.52, Found: C, 65.9; H, 8.11; N, 3.64; O, 13.7.

b) N-tert.Butyl-3-(2,6-dimethoxyphenyl)-3-phenyl-2-propene-1-amine (LXXX)

The above amine from step a) (21 g, 0.061 mol) was added to 6.3N H_2SO_4 (20 ml, 0.126 mol). The mixture was stirred on a boiling water bath for 2 h, cooled, basified, and extracted with ether. The extract was washed, dried and evaporated, giving 17.8 g, (90%) of the title olefin as a clear oil. The HCl-salt had m.p. 220°–22°, and was associated with ¼ mol of water.

$C_{21}H_{27}NO_2.HCl.¼\ H_2O$ requires: C, 68.82; H, 7.86; N, 3.82; O, 9.82; Cl, 9.68, Found: C, 68.8; H, 7.89; N, 3.92; O, 9.81; Cl, 9.44.

c) N-Methyl-N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropylamine (LXXXI), hydrogen fumarate hydrogen fumarate

The olefinic amine from step b) (16.3 g, 0.05 mol) in methanol (250 ml) containing 0.5 g of a 10% Pd/C catalyst, was hydrogenated at ambient temperature and pressure. The mixture was then filtered through Celaton, the filtrate was taken to dryness, giving 16.3 g (100%) of N-tert.butyl-3-(2,6-dimethoxyphenyl)-3-phenylpropylamine. The HCl-salt had m.p. 244° (ethanol).

$C_{21}H_{29}NO_2.HCl$ (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.3; H, 8.29; N, 3.83; O, 9.27; Cl, 9.75.

The above secondary amine, as the free base, was methylated with formaldehydeformic acid as described in Example 7, giving the tertiary amine in 96% yield. The fumaric acid salt had m.p. 185°–190° (acetone).

$C_{26}H_{35}NO_6$ (457.6) requires: C, 68.25; H, 7.71; N, 3.06; O, 20.95, Found: C, 67.8; H, 7.59; N, 3.05; O, 21.6.

EXAMPLE 9

Removal of O-protective groups

a) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (LXXXII), hydrochloride

The amine (XLIX) of Example 5k) (20.8 g, 0.064 mol) in methylene chloride (150 ml) was cooled below 0°. A 1N solution of BBr_3 in CH_2Cl_2 (64 ml, 0.064 mol) was then added dropwise, the solution was then kept in the cooler (5°) for 2–5 days, and volatile material was distilled off at <50°. The residual syrup was basified, extracted with ether, the extract was washed with water, dried and evaporated, giving a viscous syrup. The HCl-salt had m.p. 222° (methanol-ether), yield 31%.

$C_{21}H_{29}NO.HCl$ (347.9) requires: C, 72.49; H, 8.69; N, 4.03; O, 4.60; Cl, 10.19, Found: C, 72.0; H, 8.72; N, 3.74; O, 5.06; Cl, 10.3.

The following compounds were obtained in the same way.

b) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine (LXXXIII), hydrogen fumarate

From the amine (LXIV) of Example 5l). Crude yield 78%. M.p. fumaric acid salt=indefinite.

$C_{28}H_{37}O_5$ (467.6) requires: C, 71.9; H, 7.91; N, 3.00; O, 17.1, Found: C, 71.8; H, 8.41; N, 3.01; O, 16.6.

c) N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (LXXXIV), hydrochloride

From the amine (XL) of Example 5c). Crude yield 85%. HCl-salt, m.p. 209°–210° (acetone-ether).

$C_{22}H_{31}NO.HCl.¼\ H_2O$ (366.5) requires: C, 72.09; H, 8.95; N, 3.82; O, 5.46; Cl, 9.67, Found: C, 72.3; H, 8.95; N, 3.71; O, 5.68; Cl, 9.61.

d) N-Methyl-N-tert.butyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine (LXXXV), hydrochloride

From the amine (LXVI) of Example 7b). Crude yield 100%. HCl-salt, m.p. >260° (ethanol).

$C_{21}H_{29}NO.HCl$ (347.4) requires: C, 72.49; H, 8.69; N, 4.03; Cl, 10.19, Found: C, 72.7; H, 8.58; N, 3.81; Cl, 10.95.

e) N,N-Diisopropyl-3,3-bis-(2-hydroxyphenyl)-propylamine (LXXXVI), hydrochloride

From the amine (XXXVIII) of Example 5a). Crude yield 57%. HCl-salt, m.p. 257° (ethanol-ether).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.3; H, 8.37; N, 3.95; O, 9.23; Cl, 9.40.

f) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)-propylamine (LXXXVII), hydrochloride

From the amine (LXVII) of Example 7c). Crude yield 100%, m.p. 190°. HCl-salt, m.p. 252° (ethanol).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C, 68.65; H, 8.06; N, 4.00; Cl, 10.13, Found: C, 68.4; H, 8.06; N, 4.17; Cl, 9.59.

g) N,N-Diisopropyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (LXXXVIII), hydrochloride

From the amine (XLI) of Example 5d). Crude yield 90%. HCl-salt, m.p. 217° (ethanol).

$C_{22}H_{31}NO$.HCl.$\frac{1}{4}$ H_2O (366.5) requires: C, 72.09; H, 8.96; N, 3.82; O, 5.46; Cl, 9.67, Found: C, 72.3; H, 8.91; N, 3.93; O, 5.27; Cl, 9.46.

h) N,N-Diisopropyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (LXXXIX), hydrochloride

From the amine (XLII) of Example 5e). Crude yield 93%, m.p. 166°. HCl-salt, m.p. 220° (ethanol).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C, 70.47; H, 8.74; N, 3.57; Cl, 9.05, Found: C, 70.6; H, 8.78; N, 3.71; Cl, 8.93.

i) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (XC), hydrochloride

From the amine (LXIX) of Example 7e). Crude yield 79%, m.p. 199°–201° (IPE). HCl-salt, m.p. 220° (acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, 69.9; H, 8.70; N, 3.75; O, 8.81; Cl, 9.15.

j) N-Methyl-N-tert.butyl-3-(2-hydroxy-4-methylphenyl)-3-phenylpropylamine (XCI), hydrochloride

From the amine (LXVIII) of Example 7d). Crude yield 100%. HCl-salt, m.p. 240° (ethanol).

$C_{21}H_{29}NO$.HCl (347.9) requires: C, 72.49; H, 8.69; N, 4.03; O, 4.60; Cl, 10.19, Found: C, 72.51 H, 8.75; N, 4.06; O, 4.90; Cl, 10.1.

k) N,N-Diisopropyl-3-(4-fluorophenyl)-3-(2-hydroxyphenyl)propylamine (XCII), hydrochloride

From the amine (XLVII) of Example 5j). Crude yield 72%. HCl-salt, m.p. 183° (acetone-ethanol).

$C_{21}H_{27}FNO$.HCl (364.9) requires: C, 69.12; H, 7.73; N, 3.83, Found: C, 69.1; H, 8.09; N, 3.82.

l) N,N-Diisopropyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCIII), hydrochloride

From the amine (XLV) of Example 5h). Crude yield 31%. HCl-salt, m.p. 205°–210° (ethanol-acetone-ether).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.5; H, 8.33; N, 3.72; O, 8.91; Cl, 9.87.

m) N-(1,1-Dimethylpropyl)-N-methyl-3,3-bis-(2-hydroxy-5-methylphenyl)propylamine (XCIV), hydrochloride

From the amine (LXXII) of Example 7h). Crude yield 100%, m.p. 190°–195°. HCl-salt, m.p. 235°–240° (ethanol-acetone-ether).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C, 70.47; H, 8.74; N, 3.57; O, 8.16; Cl, 9.05, Found: C, 70.0; H, 8.96; N, 3.54; O, 8.11; Cl, 9.19.

n) N-Methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine (XCV), hydrobromide

From the amine (LXXIII) of Example 7i). Crude yield 78%, m.p. 260°. HBr-salt, m.p. >260° (ethanol).

$C_{20}H_{25}NO_2$.HBr (394.4) requires: C, 60.9; H, 7.16; N, 3.55; O, 8.11; Br, 20.27, Found: C, 60.8; H, 7.18; N, 3.29; O, 8.38; Br, 20.2.

o) N,N-Diisopropyl-3,3-bis-(2,4-dihydroxyphenyl)-propylamine (XCVI), hydrochloride

From the amine (XLVI) of Example 5i). The HCl-salt, consisting of an amorphous brown powder, did not give a satisfactory elemental analysis because of incomplete combustion.

p) N-Methyl-N-tert.butyl-3,3-bis-(2,4-dihydroxyphenyl)propylamine (XCVII), hydrochloride

From the amine (LXXVI) of Example 7l). Crude yield 87%, m.p. 260°. The HCl-salt did not give a satisfactory elemental analysis because of incomplete combustion.

q) N,N-Diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCVIII), hydrochloride

The amine (XLIII) of Example 5f) in the form of the free base (32 g, 0.063 mol) in methanol (500 ml) containing 5 g of a 5% Pd/C catalyst was hydrogenated at ambient temperature and pressure. After 2 h the reaction was complete. The mixture was filtered, the filtrate was taken to dryness, the residue was dissolved in acetone and treated with ethereal HCl, giving 19.8 g (87%) of a crude salt, m.p. 260°. Recrystallization from methanol gave white crystals, m.p. 260°.

$C_{21}H_{29}NO_2$.HCl $\frac{1}{4}$ H_2O (368.6) requires: C, 68.44; H, 8.36; N, 3.80; O, 9.77; Cl, 9.62, Found: C, 68.4; H, 8.40; N, 3.60; O, 10.3; Cl, 9.42.

The following compounds were prepared in the same way.

r) N-Methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine (XCIX), hydrochloride

From the amine (LXXIV) of Example 7j). Crude yield 90%. HCl-salt, m.p. >270° (methanol-water).

$C_{20}H_{27}NO_2$.HCl (349.9) requires: C, 68.65; H, 8.06; N, 4.00; O, 9.14; Cl, 10.13, Found: C, 68.9; H, 8.02; N, 3.93; O, 9.60; Cl, 10.5.

s) N,N-Diisopropyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (C), hydrochloride

From the amine (XLIV) of Example 5g). Crude yield 100%. HCl-salt, m.p. 253° (methanol-ether).

$C_{23}H_{33}NO_2$.HCl (392.0) requires: C, 70.47; H, 8.74; N, 3.57; O, 8.16; Cl, 9.05, Found: C, 70.5; H, 8.74; N, 3.55; O, 8.47; Cl, 8.03.

t) N-Methyl-N-tert.butyl-3,3-bis-(2-hydroxy-4-methylphenyl)propylamine (CI), hydrochloride

From the amine (LXXV) of Example 7k). Crude yield 97%, a yellow powder.HCl-salt, m.p. 260° (methanol-acetone).

$C_{22}H_{31}NO_2$.HCl (378.0) requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, 69.9; H, 8.68; N, 3.67; O, 8.85; Cl, 9.24.

u) N,N-Diisopropyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CII), hydrochloride

From the amine (XXXIX) of Example 5b). Crude yield 100%. HCl-salt, m.p. 174°–176° (acetone).

$C_{21}H_{29}NO_2$.HCl (363.9) requires: C, 69.31; H, 8.31; N, 3.85; O, 8.79; Cl, 9.74, Found: C, 69.5; H, 8.33; N, 3.66; O, 9.37; Cl, 9.63.

w) N-Methyl-N-tert.butyl-3-(2,3-dihydroxyphenyl)-3-phenylpropylamine (CIII), hydrochloride

From the amine (LXXVII) of Example 7m). Crude yield 100%, a white powder.HCl-salt, m.p. 209°–210°, slow heating, (methanol-acetone).

$C_{20}H_{27}NO_2.HCl.\frac{1}{4}H_2O$ (358.9) requires: C, 66.92; H, 8.14; N, 3.90; O, 11.14; Cl, 9.88, Found: C, 66.9; H, 8.12; N, 3.76; O, 11.8; Cl, 9.74.

x) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (CIV), hydrochloride

From the amine (LXXVIII) of Example 7n). Crude yield 100%. HCl-salt, m.p. 255° (acetone-ether).

$C_{20}H_{27}NO.HCl$ (333.9) requires: C, 71.94; H, 8.45; N, 4.20; Cl, 10.62, Found: C, 71.9; H, 8.43; N, 4.01; Cl, 10.5.

y) N-Methyl-N-tert.butyl-3-(2,6-dihydroxyphenyl)-3-phenylpropylamine (CV), hydrochloride

From the amine (LXXXI) of Example 8c) with BBr_3, in low yield. HCl-salt, m.p. 170° (ethanol-ether).

$C_{20}H_{27}NO_2.HCl.\frac{1}{2}H_2O$ (358.9) requires: C, 66.93; H, 8.14; N, 3.40; O, 11.14; Cl, 9.87, Found: C, 67.4; H, 8.28; N, 3.63; O, 10.9; Cl, 9.99.

z) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The base from Example 5m) (11.7 g, 0.032 mol) was treated with pyridine (7.6 g, 0.096 mol) and conc. HCl (13 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205°–215° for 1½ h. The melt was cooled somewhat, water was added, the mixture was digested in a boiling water bath and cooled. 2N HCl was added, the salt was filtered off, washed with 2N HCl and dried, giving 11.0 g (90%) white salt m.p. 200° . Recrystallization from acetone gave the hydrochloride of the title compound, m.p. 202°–203°.

$C_{21}H_{28}ClNO.HCl$ (382.4) requires: C, 65.96; H, 7.64; N, 3.66; Cl, 18.54, Found: C, 66.0; H, 7.88; N, 3.63; Cl, 18.3.

aa) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

The free base from Example 7o) (10.5 g, 0.03 mol) was treated with pyridine (7.0 g, 0.09 mol) and conc. HCl (12 g). The mixture was taken to dryness in vacuum and the residue was heated in an oil-bath at 205°–215° for 1½ h. The melt was cooled somewhat, excess of 2N NaOH was added, the mixture was extracted with ether, the extract was washed with water, dried and evaporated giving 7.5 g (88%) crude syrup. This was dissolved in ether and treated with ethereal HCl giving 8 g (83%) of hydrochloride salt. Recrystallization from acetone-2N HCl gave the hydrochloride of the title compound, m.p. 260°.

$C_{20}H_{26}ClNO.HCl$ (368.4) requires: C, 65.21; H, 7.39; N, 3.80; Cl, 19.25, Found: C, 65.0; H, 7.30; N, 3.73; Cl, 18.9.

ab) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-2,2,5,5-tetramethylpyrrolidine

The crude amine from Example 5n) was hydrogenolysed as described in Example 9q). The free amine was obtained as an oil which was converted to the hydrochloride and crystallized from 2-propanol. M.p. 250° C.

$C_{23}H_{31}NO.HCl$ (374.0) requires: C, 73.86; H, 8.63; N, 3.75; O, 4.28; Cl, 9.48, Found: C, 73.8; H, 8.71; N, 3.59; O, 4.80; Cl, 9.45.

ac) N-(3-(2-Hydroxyphenyl)-3-phenylpropyl)-4-hydroxy-2,2,6,6-tetramethylpiperidine

The benzyloxy compound from Example 5o) was hydrogenolysed as described in Example 9q). The free base was converted to the hydrochloride semihydrate which was crystallized from acetone. The compound melts with decomposition at about 150° C.

$C_{24}H_{33}NO_2.HCl.\frac{1}{2}H_2O$ (413.0) requires: C, 69.79; H, 8.54; N, 3.39; O, 9.68; Cl, 8.58, Found: C, 70.0; H, 8.67; N, 3.47; O, 9.98; Cl, 8.13.

ad) N-(2-Hydroxy-1,1-dimethylethyl)-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7p) was hydrogenolysed as described in Example 9q). The amine, obtained as a glassy mass, was converted to the hydrochloride which was obtained as an amorphous solid on precipitation from ethanol with ether.

$C_{20}H_{27}NO_2.HCl$ (349.9) requires: C, 68.65; H, 8.06; N, 4.00; O, 9.15; Cl, 10.13, Found: C, 68.25; H, 8.18; N, 3.98; O, 9.12; Cl, 10.0.

ae) N-1-Adamantyl-N-methyl-3-(2-hydroxyphenyl)-3-phenylpropylamine

The benzyloxy compound from Example 7q) was hydrogenolysed as described in Example 9q). The free hydroxyamine was obtained as a glassy mass. It was dissolved in anhydrous ether and treated with an excess of hydrogen chloride in ether. The hydrochloride precipitated as a powder which decomposed at about 220° C.

$C_{26}H_{33}NO.HCl$ (412.0) requires: C, 75.79; H, 8.32; N, 3.40; O, 3.88; Cl, 8.61, Found: C, 75.3; H, 8.01; N, 3.22; O, 3.45; Cl, 8.96.

EXAMPLE 10

Reduction of amides

a) N,N-Diisopropyl-3- (2-methoxy-5-methylphenyl)-3-phenylpropylamine

3-(2-Methoxy-5-methylphenyl)-3-phenylpropionic acid (12.8 g, 0.05 mol) (J. D. Simpson & H. Stehphen, J. Chem. Soc. 1956 1382) and thionyl chloride (50 ml) are heated on a water bath for 3 h. The excess of thionyl chloride is distilled off under reduced pressure. The remaining crude 3-(2-methoxy-5-methylphenyl)3-phenylpropionyl chloride is dissolved in 50 ml of dichloromethane and added dropwise to a stirred solution of diisopropylamine (20.2 g, 0.20 mol) in 200 ml of dichloromethane at about 0° C. The solution is left for 2 h, the solvent is distilled off and the remaining material is treated with water. The solid product consisting of N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropionamide is filtered off, dried and added in small portions to a stirred suspension of lithium aluminium hydride (6.0 g, 0.16 mol) in dry ether (700 ml). The mixture is refluxed for 2 days. Excess of hydride is destroyed by the careful addition of water, the ether layer is separated and dried with anhydrous sodium sulfate. After filtration the solution is added to a solution of excess fumaric acid in ether. The precipitated salt is collected and crystallized from 2-propanol. The hydrogen fumarate melts at 176° C.

b) N-Methyl-N-tert.butyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine was similarly prepared. The hydrochloride melts at 161° C.

EXAMPLE 11

a) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine

A solution of chlorine (7,1 g, 0,10 mol) in acetic acid (500 ml) is added dropwise to a stirred solution of N-methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3 -phenylpropylamine (29.7 g. 0.10 mol) in acetic acid (200 ml) with stirring. After 2 h the solvent is distilled off under reduced pressure and the crude hydrochloride left is recrystallized from 2-propanol. Melting point 260° C.

b) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared. The hydrochloride melts at 202°–3° C.

EXAMPLE 12

Separation of(+)- and (−)-enantiomers

(±)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine (31.1 g, 0.10 mol) is dissolved in 300 ml of ethanol. A solution of L(+)-tartaric acid (15.0 g, 0.10 mol) in 400 ml of ethanol is added. The mixture is heated a few minutes in a boiling water bath and seeded with crystals obtained by cooling and scratching a small sample of the main solution. The mixture is chilled at about 4° C. over-night whereupon the crystalline precipitate is filtered off, washed with cold ethanol and recrystallized repeatedly from ethanol. The pure (−)-N,N-diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine hydrogen L-(+)-tartrate thus obtained has $[\alpha]_D^{20}-10.6°$ (c=5% in methanol). The free amine is obtained by alkalisation of an aqueous solution, extraction into ether, drying and evaporation of the solvent. Sticky oil, $[\alpha]_D^{20}-5.4°$ (c=5% in methanol).

(+)-N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-phenylpropylamine is similarly prepared using D-(−)-tartaric acid. The hydrogen-D-(−)tartrate has $[\alpha]_D^{20}+10.0°$. The free amine has $[\alpha]_D^{20}+5.6°$, both measured as 5% solutions in methanol.

EXAMPLE 13 (CONTINUATION OF EXAMPLE 1)

Preparation of 4-phenyl-3,4-dihydrocoumarins

g) 4-(2-Methoxyphenyl)6-methyl-3,4-dihydrocoumarin (CIV)

A mixture of 2-methoxycinnamic acid (178 g, 1.0 mol), p-cresol (108 g, 1.0 mol), and p-touenesulphonic acid monohydrate (47.5 g, 0.25 mol) was stirred on a boiling water-bath for about 2 h during which time the system was evacuated with a waterpump to remove formed water. The solid was then broken up and washed copiously with water. The granular material was then stirred with a large volume of saturated $NaHCO_3$ solution containing some 10% acetone. The product was filtered off, washed dried and recrystallised from acetone affording 167 g (62,5%) white crystals of the desired lactone, m.p. 140°.

$C_{17}H_{16}O_3$ (268.3) requires: C, 76.10; H, 6.01; O, 17.89, Found: C, 76.0; H, 5.97; O, 17.9.

h) 6-Chloro-4-(2-methoxyphenyl)-3,4-dihydrocoumarin (CVII) was prepared in a similar way in 49% yield from 2-methoxycinnamic acid and p-chlorophenol, the reaction temperature being 130° in this case. M.p. 172°–173° (acetone).

$C_{16}H_{13}O_3$ (288.7) requires: C, 66.56; H, 4.54; O, 16.62, Found: C, 66.8; H, 4.45; O, 16.5.

EXAMPLE 14 (CONTINUATION OF EXAMPLE 2)

Preparation of 3,3-diphenylpropionic acid esters

l) Methyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propionate (CVIII) was obtained as an oil in 75% yield from the lactone CVI of Example 13g in the manner described for the ester VI of Example 2a).

m) Methyl-3-(5-chloro-2-methoxyphenyl)-3-(2methoxyphenyl)propionate (CIX) was obtained as an oil in the same way in 97% yield from the lactone CVII of Example 13.

EXAMPLE 15 (CONTINUATION OF EXAMPLE 3)

Preparation of 3,3-diphenylpropanols

m) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propanol (CX) was obtained in 84% yield from the ester CIX of Example 14m in the manner described for the propanol XVI of Example 3a), except that the reduction was carried out in toluene with a 10% molar excess of a 3.4M toluenic solution of sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH) instead of $LiAlH_4$. M.p. 70°–72°(IPE).

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propanol (CXI) was obtained in the same way in quantitive yield from the ester CVIII of Example 141). The product consisted of a golden oil of 89% purity according to GC.

EXAMPLE 16 (CONTINUATION OF EXAMPLE 4)

Preparation of 3,3-diphenylpropyl-p-toluenesulphonates

n) 3-(2-Methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propyl-p-toluene-sulphonate (CXII) was prepared in the same way as the tosylate XXVII of Example 4a) in quantitative yield from the propanol CXI of Example 15n) using CH_2Cl_2 as solvent instead of chloroform. M.p. 101° (ether/IPE).

$C_{25}H_{28}O_5S$ (440.57) requires: C, 68.16; H, 6.41; S, 7.28, Found: C, 68.3; H, 6.51; S, 7.20.

o) 3-(5-Chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propyl-p-toluenesulphonate (CXIII) was obtained in the same way in quantitative yield from the propanol CX of Example 15m. M.p. 97°–98° (acetone-/IPE).

$C_{24}H_{25}ClO_5S$ (460.92) requires: C, 62.54; H, 5.47; S, 6.94; Cl, 7.69, Found: C, 63.0; H, 5.65; S, 6.95; Cl, 7.70.

EXAMPLE 17 (CONTINUATION OF EXAMPLE 5)

Preparation of tertiary 3,3-diphenylpropylamines

r) N,N-Diisopropyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXIV) was obtained as an oil in 94% yield from the tosylate CXIII of Example 16o) in the manner described for the amine XXXVIII of Example 5a). Purity by GC=99.9%.

s) N,N-Diisopropyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXV) was obtained in the same way in 49% crude yield from the tosylate CXV of Example 16n). After chromatographic purification on an Si-gel 60 column (eluation with light petroleum), the product (oil) had a purity of 100% according to GC.

t) N-[(2-Benzyloxy-5-methyl)-3-phenyl]-2,2,5,5-tetramethylpyrrolidine (CXVI) was prepared from 3-(2-benzyloxy-5-methyl)-3-phenylpropyl tosylate and 2,2,5,5-tetramethylpyrrolidine following the directions given in Example 5a). It was obtained as a sticky oil which was converted to the free hydroxy compound of Example 20aj).

EXAMPLE 18 (CONTINUATION OF EXAMPLE 6)

Preparation of secondary 3,3-diphenylpropylamines

p) N-tert.Butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXVII) was prepared in

quantitative yield from the tosylate CXIII of Example 16o) in the manner described for the amine L of Example 6a). The HCl-salt had m.p. >260°.

$C_{21}H_{28}ClNO_2.HCl$ (398.38) requires: C, 63.3; H, 7.34; N, 3.52; Cl, 17.80, Found: C, 63.2; H, 7.46; N, 3.49; Cl, 17.4.

q) N-tert.Butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXVIII) was obtained in a similar way in 89% crude yield from the tosylate CXII of Example 16n). The HCl-salt had m.p. 225°.

$C_{22}H_{31}O_2N.HCl$ (377.97)

Requires: C, 69.91; H, 8.54; N, 3.71; Cl, 9.38; O, 8.47, Found: C, 69.8; H, 8.73; N, 3.60; Cl, 9.45; O, 8.79.

EXAMPLE 19 (CONTINUATION OF EXAMPLE 7)

Preparation of tertiary 3,3-diphenylpropylamines from secondary amines

r) N-Methyl-N-tert.butyl-3-(5-chloro-2-methoxyphenyl)-3-(2-methoxyphenyl)propylamine (CXIX) was prepared in 89% yield from the amine CXVII of Example 18p) in the manner described for the amine LXI of Example 7a). The HCl-salt was prepared by treating an acetonic solution of the free base with conctrated hydrochloric acid. M.p. 130°.

$C_{22}H_{30}ClO_2N.HCl.H_2O$ (430.42)

Requires: C, 61.39; H, 7.74; N, 3.25; Cl, 16.47, Found: C, 62.0; H, 7.93; N, 3.26; Cl, 16.5.

s) N-Methyl-N-tert.butyl-3-(2-methoxyphenyl)-3-(2-methoxy-5-methylphenyl)propylamine (CXX) was prepared in a similar way in 98% yield from the amine CXVIII of Example 18q). The free base (oil) had a purity of 96% by GC.

EXAMPLE 20 (CONTINUATION OF EXAMPLE 9)

Removal of O-proptective groups

af) N,N-Diisopropyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methylphenyl)propylamine (CXXI)

The amine CXV from Example 17s) (26.5 g, 0.072 mol) in methanol was treated with a slight excess of concentrated hydrochloric acid. The mixture was taken to dryness in vacuum, pyridinium chloride (25.4 g, 0.22 mol) was added and the mixture was then heated at 200°–205° for 1½ h. The mixture was cooled to about 80°, acetone (20 g) was added followed by addition of little water. The salt was filtered off, washed with diluted HCl and dried. Recrystallisation from absolute ethanol/ether gave 17.5 g (64.3%) of a white salt, m.p. >250°. Purity by GC=100%.

$C_{22}H_{31}NO_2.HCl$ (377.97) Requires: C, 69.91; H, 8.54; N, 3.71; O, 8.47; Cl, 9.38, Found: C, 69.8; H, 8.65; N, 3.57; O, 8.76; Cl, 9.51.

ag) N,N-Diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)propylamine (CXXII was prepared in the same way in 37% yield from the amine CXIV of Example 17r). The HCl-salt had m.p. 214° (ethanol).

$C_{21}H_{28}NO_2.HCl$ (398.38) Requires: C, 63.31; H, 7.34; N, 3.52; O 8.03; Cl, 17.80, Found: C, 63.1; H, 7.34; N, 3.40; O, 8.15; Cl, 17.8.

ah) N-Methyl-N-tert.butyl-3-(2-hydroxyphenyl)-3-(2-hydroxy-5-methylphenyl)propylamine (CXXIII) was prepared in the same way in 30% yield from the amino CXX of Example 19s). The HCl-salt had m.p. 240° (acetone).

$C_{21}H_{29}NO_2.HCl$ (363.94) requires: C, 69.3; H, 8.31; N, 3.58; Cl, 9.74, Found: C, 69.0; H, 8.35; N, 3.65; Cl, 9.76.

ai) N-Methyl-N-tert.butyl-3-(5-chloro-2-hydroxyphenyl)-3-(2-hydroxyphenyl)propylamine (CXXIV) was prepared in the same way in 24% yield from the amine CXIX of Example 19r). M.p. >250°.

$C_{20}H_{26}ClNO_2.HCl$ (384.36) requires: C, 62.50; H, 7.08; N, 3.65; Cl, 18.45, Found: C, 62.5; H, 7.09; N, 3.63; Cl, 18.4.

aj) N-[3-(2-Hydroxy-5-methylphenyl)-3-phenylpropyl]-2,2,5,5-tetramethylpyrrolidine (CXXV) was obtained when the O-benzylated amine CXVI of Example 17t) was hydrogenolyzed as described in Example 9q. The hydrochloride melts at 240°.

$C_{24}H_{34}ClNO$ (388.0) requires: C, 74.29; H, 8.83; N, 3.61; Cl, 19.14, Found: C, 73.9; H, 8.90; N, 3.52; Cl, 9.48.

EXAMPLE 21 (CONTINUATION OF EXAMPLE 10)

Reduction of amides

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamine

N,N-Diisopropyl-3-(2-methoxyphenyl)-3-phenylpropionamide was obtained as o pale yellow oil in quantitative yield from 3-(2-methoxyphenyl)-3-phenylpropionic acid in the manner described for the amide of Example 10a). This amide (27 g, 0.08 mol) in toluene (50 g) was added dropwise under r.t. to a 3.4M toluenic solution of SMEAH (50 g, 0,17 mol) diluted with an equal weight of toluene. The mixture was stirred at 60°–70° for 2 h, cooled, treated with excess od 2N NaOH. The organic phase was separated, washed with water and extracted with 2N HCl. The acidic extract was washed with ether, basified, extracted with ether, dried and evaporated giving 17.1 g (66%) free base. This was dissolved in acetone (75 ml) and treated with 6.6 g fumaric acid dissolved in methanol, affording 20 g of the fumaric acid salt, m.p. 163°–164°.

$C_{22}H_{31}ON.C_4H_4O_4$ (441.58) requires: C, 70.72; H, 7.99; N, 3.17; O, 18.12, Found: C, 70.7; H, 7.96; N, 3.13; O, 18.0.

EXAMPLE 22

Separation of (+)- and (−)-enantiomers

(+)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen tartrate

The racemic amine (LXXXVIII of Example 9g) (48.8 g, 0.15 mol) was dissolved in 500 ml of 95% ethanol and mixed with a solution of L(+)-tartaric acid (22.5 g, 0.15 mol) in 500 ml of ethanol. The mixture was left over night at +4°. The precipitated salt was collected by filtration and washed with ethanol and ether. The yield of crude salt with $[\alpha]_{546}^{25}$ +29.5° (C 5%, methanol) was 34,3 g. Two recrystallisations from ethanol afforded 21.8 g with $[\alpha]_{546}^{25}$ +36.0°.

$C_{26}H_{37}NO_7$ requires: C, 65.66; H, 7.84; N, 2.95; O, 23.55, Found: C, 65.9; H, 8.06; N, 2.90; O, 23.5.

(−)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine hydrogen D(−)-tartrate was similarly prepared using D(−)-tartaric acid.

$[\alpha]_{546}^{25}$ −35.8°.

Found: C, 65.6; H, 8.00; N, 2.83; O, 23.6.

Several of the compounds according to the invention were tested with regard to anti-cholinergic, anti-noradrenaline, and anti-calcium effects, toxicity and effect

on the heart rate. The test procedures are described below, and the test results are reported in Table 1. For comparison purposes the testing also included the commercially available drug terodiline and a structurally similar compound, N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, disclosed as an antidepressant in U.S. Pat. No. 3,446,901, GB-A-1.169.944, and GB-A-1.169.945. The test results clearly show that the compounds according to the invention are superior to the known compounds especially as regards selectively between the desired anti-cholinergic activity and the undesired side-effects.

a) Anticholinergic activity on isolated urinary bladder

Male guinea-pigs, weighing 250–350 g, were killed by a blow on the head and exsanguinated. The urinary bladders were quickly removed and placed in Na+-Krebs, in which they were kept throughout the dissection procedure. The bladders were dissected free from adherent fat and connective tissue before they were cut open by an incision on each side from the base towards apex. The mucosa was carefully removed with a pair of scissors. Four strips, approximately 3–5 mm long were prepared by cutting in a parallel direction to the longitudinal muscle fibers, on each half of the bladder.

The bladder strips were immediately mounted vertically in 5 ml organ baths containing Na+-Krebs solution aerated with carbogene gas to maintain the pH at about 7.4. The temperature, 37° C., was thermostatically controlled by a Lauda MS3 thermostatic circulator. The preparations were suspended between two hooks, one of which was connected to a Grass Instruments FTO3 force transducer. The isomeric tension of the preparations was recorded by a Grass polygraph model 79D. The resting tension was applied to approximately 5 mN. The strips were allowed to stabilize for at least 45 minutes. During this period the resting tension was adjusted to 5 mN and the preparations were repeatedly washed.

In the preliminary experiments concentration-effect curves for carbachol (carbamylcholin chloride) were studied, in order to determine a suitable agonist concentration for inhibition studies with antagonist. The carbachol concentration chosen, 3×10^{-6}M, produced a submaximal contractant response (70%). In the inhibition studies, the strips were contracted with carbachol (3×10^{-6}M) every 15 minutes. The strips were washed three times after every agonist addition. This procedure was repeated until a reproducible contractant response was observed. A variation of about 10% for three subsequent contractions was accepted as reproducible.

Initially each antagonist was tested in a concentration of 10^{-6}M, on two bladder-strips from different guinea-pigs. When a reproducible response with 3×10^{-6}M carbachol was obtained, the strips were incubated with the antagonist for 15 minutes before the next carbachol was added. If the antagonist produced more than 50% inhibition of the response to carbachol, a complete concentration-inhibition curve was also made. In the complete inhibition curves, the strips were then incubated for 60 minutes with a fixed concentration of the antagonist before the next addition of carbachol. The effect of the antagonists was calculated as per cent inhibition of the mean of the initial agonist-induced contractions. To generate concentration-inhibition curves the antagonists were studied in 6–8 concentrations and for each concentration a fresh preparation was used, i.e. the strips were only exposed to the antagonist once before they were discarded.

b) Antagonistic effect to noradrenaline and calcium on the portal vein Preparation of isolated portal vein from rat

Animals: Albino, male rats, weighing about 200 g.
Bath volume: 5 ml
Buffer: Na+-Krebs, modified by K. E. Andersson
Temperature: 37° C.
Gas: Carbogene (93.5% O_2+6.5% CO_2)
Muscle tension: 0.5 g

The rat is killed by a blow on the neck and decapitated. The abdomen is opened, the vein is dissected free from fat, cut open longitudinally and mounted in an organ bath. Changes in isometric tension is registered by a force displacement transducer, connected to an amplifier and a writing oscillograph.

Noradrenaline-antagonism on portal vein

Doses: Noradrenaline 3×10^{-7}M

The chosen doses give about 70% of maximal response. The agonist is added to the bath at 10-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 10 minutes noradrenaline is added. The next concentration of the test substance is added when the original response of the agonist is obtained.

The antagonistic effect of the substance is calculated as per cent inhibition of the mean response by three preceding doses of the agonist.

Ca-antagonistic effect on portal vein

10 mM K+-solution is added to the Krebs buffer to stabilize the spontaneous myogenic activity of the vein. The amplitude of the muscle contractions is measured. The test substance is added to the bath in cumulative doses until total inhibition is obtained.

c) Histamine-antagonism on isolated ileum

Preparation of isolated ileum from guinea pigs

Animals: Guinea pigs of both sexes, weighing about 350 g.
Bath volume: 5 ml
Buffer: Na+-Krebs, modified by K. E. Andersson
Temperature: 37° C.
Gas: Carbogene (93.5% O_2+6.5% CO_2)
Muscle tension: 0.5 g

The guinea pig is killed by a blow on the neck and decapitated. The abdomen is opened and about 2 cm of the ileum is cut off about 15 cm above the ileocaecal junction. The piece of ileum is washed with buffer and mounted in an organ bath. Changes in isometric tension is recorded by a force displacement transducer, connected to an amplifier and a writing oscillograph.

Dose: 5×10^{-7}M of histamine.

The chosen dose of histamine gives about 70% of maximal response. The agonist is added to the bath at 3-minutes intervals. When reproducible contractions are obtained a fixed concentration of the test substance is added to the bath. After an incubation period of 2–10 minutes a new contraction is induced by histamine. The next concentration of the test substance is added when the original response of the agonist is obtained.

The agonistic effect of the test substance is calculated as per cent inhibition of the mean response by three preceding doses of histamine.

d) Acute toxicity in mice

The antagonists to be tested were dissolved in 0.9% NaCl. If they were not soluble in 0.9% NaCl they were dissolved in double distilled water. The solutions were prepared on the day of the experiment.

Procedure

White male mice, 25 g, were placed in a mouse holder. The tested compounds were given as i.v. bolus doses in one of the four tail-veins, with a volume of 0.01 ml/g mouse. Each substance concentration was given to a group of four mice. 4–5 different concentrations of the antagonists were made and tested.

The acute lethal dose (LD_{11}) was the lowest concentration of the anticholinergic drug where 4 mice of 4 tested died within 5 minutes after an i.v. bolus dose.

LD_{50}-interval: The LD_{50}-interval was between the highest dose where 4 mice survived and the lowest dose where 4 mice died within 5 minutes after an i.v. bolus dose.

e) Effect on heart rate in conscious rat

The animal is slightly anaestetized by ether and an infusion cannula is inserted into a tail vein. While still asleep the rat is placed in a simple device, made of a coarse, somewhat elastic net fixing the rat in a constant position. Electrodes are attached to the extremities and connected to an ECG-pulse pre-amplifier and a Grass polygraph. By recording the ECG, the heart rate can then be determined.

Before any substance is given the animal has regained consciousness and the heart rate has been constant for at least 15 minutes.

The substance is injected, i.v. in the infusion cannula and flushed with physiological saline.

ECG is recorded 0.25, 0.5, 1, 2, 3 and 5 minutes after completed injection and then every 5 minutes until the original heart rate is obtained.

TABLE 1

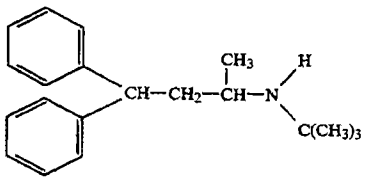
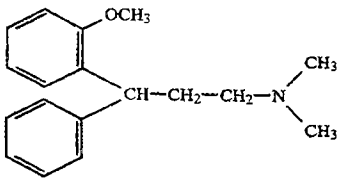
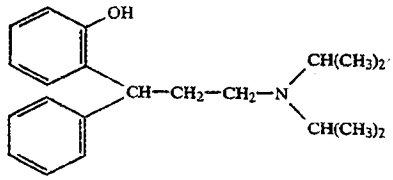
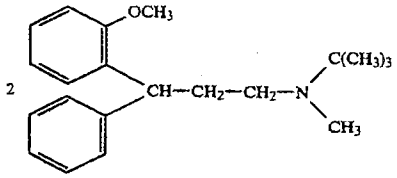
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
 Terodiline (prior art)	5.2×10^{-7}	2.4×10^{-6}	10^{-5}	4×10^{-6}	15–20	20	1–3
 GB-A-1.169.944 (antidepressant)	1.2×10^{-6}	4.4×10^{-6}	2.1×10^{-5}	3.7×10^{-7}	10–15	15	
1  Racemate	1.8×10^{-8}	10^{-5}	1.5×10^{-5}	7×10^{-6}	10–20	20	1–3
1a (+)-isomer of 1	1.8×10^{-8}						
1b (−)-isomer of 1	1.4×10^{-8}						
2 	1.5×10^{-7}	3.5×10^{-6}	9×10^{-6}		10–20	20	

TABLE 1-continued

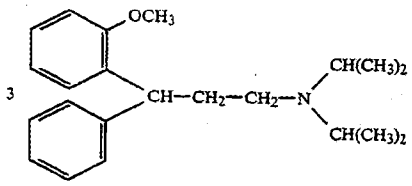
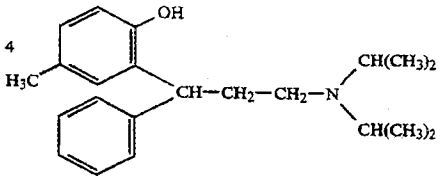
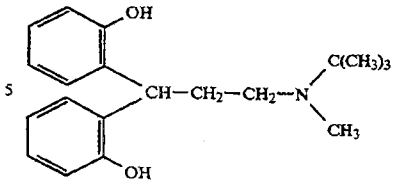
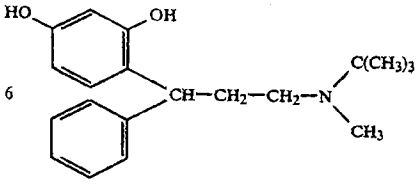
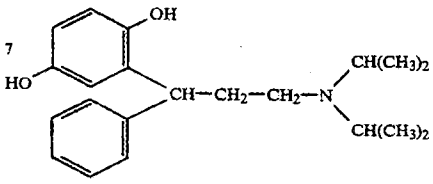
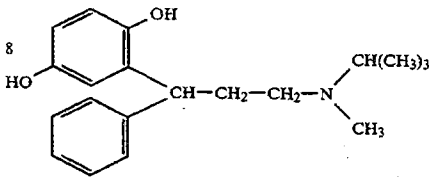
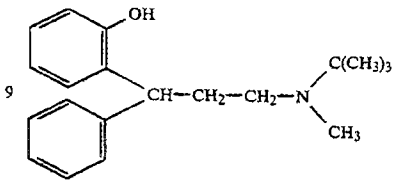
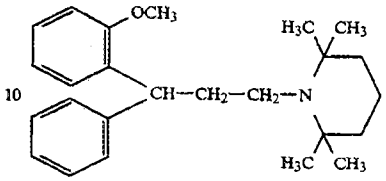
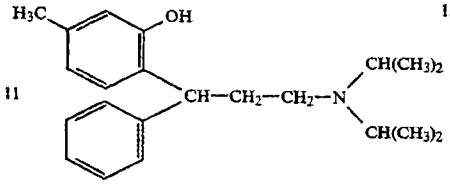
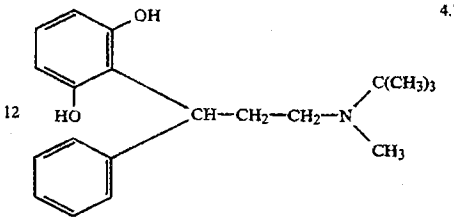
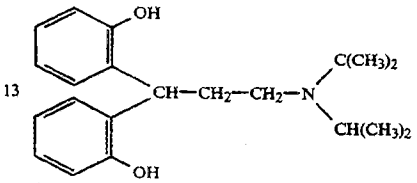
Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
3 	2.4×10^{-7}	3.6×10^{-6}	$>10^{-4}$		3–10	10	
4 	1.5×10^{-8}	5.5×10^{-6}	6×10^{-6}	10^{-5}	30–40	40	
4a. (+)-isomer of 4-tartrate	1.3×10^{-8}		6.5×10^{-6}		10–20	20	
4b. (−)-isomer of 4-tartrate	1.3×10^{-6}		6×10^{-6}		10–20	20	
5 	4.9×10^{-9}	3.8×10^{-5}	3×10^{-5}	10^{-5}	30–45	45	1–3
6 	2.0×10^{-7}	3×10^{-5}	6.5×10^{-5}	1.3×10^{-5}	>20	>20	
7 	1.9×10^{-8}	5×10^{-5}	6.5×10^{-5}	3×10^{-6}	30–50	50	
8 	3.1×10^{-8}	5×10^{-5}	$>5 \times 10^{-5}$	7×10^{-6}	>6	>6	

TABLE 1-continued

Substance	Antichol. effect IC_{50} (M)	Anti-N.A. effect IC_{50} (M)	Anti-Ca effect IC_{50} (M)	Anti-HI effect IC_{50} (M)	Acute toxicity i.v. mg/kg	Lethal dose mg/kg	Effect on heart rate threshold dose mg/kg
9 	1.6×10^{-8}	5×10^{-5}	2.5×10^{-5}	1.2×10^{-6}		20	
10 	6.2×10^{-8}	4×10^{-6}	7×10^{-6}	2.5×10^{-6}			
11 	1.0×10^{-8}	5.5×10^{-6}	10^{-5}	2.5×10^{-6}	10-20	20	
12 	4.7×10^{-7}		2.3×10^{-5}	8.0×10^{-6}	15-30	30	
13 	9.0×10^{-9}	3×10^{-5}	1.5×10^{-5}	2×10^{-5}	5-10	10	

EXAMPLE A

Preparation of tablets

Ingredients	mg/tablet
1. Compound 1 in Table 1	2.0
2. Cellulose, microcrystalline	57.0
3. Calcium hydrogen phosphate	15.0
4. Sodium starch glycolate	5.0
5. Silicon dioxide, colloidal	0.25
6. Magnesium stearate	0.75
	80.0 mg

The compound 1 according to the invention is mixed with ingredients 2, 3, 4 and 5 for about 10 minutes. The magnesium stearate is then added, the resultant mixture being mixed for about 5 minutes and then compressed into tablet form with or without filmcoating.

EXAMPLE B

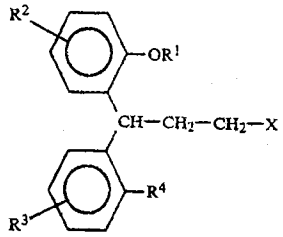
Preparation of capsules

Ingredients	mg/capsule
1. Compound 1 in Table 1	2
2. Lactose	186
3. Corn starch	20
4. Talc	15
5. Magnesium stearate	2
	225 mg

The compound 1 according to the invention is mixed with ingredients 2 and 3 and then milled. The resulting mixture is then mixed with ingredients 4 and 5 and then filled into capsules of appropriate size.

We claim:

1. 3,3-Diphenylpropylamines of formula I



I

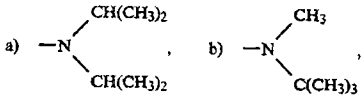
wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II

II

wherein each of R^5 and R^6 independently signifies C_{1-6}alkyl, which may be joined to form a non-aromatic ring having no hetero atom other than the amine nitrogen and each of which may carry a hydroxy substituent, or adamantyl, and wherein R^5 and R^6 together contain at least four carbon atoms, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. 3,3-Diphenylpropylamines according to claim 1, wherein at least one of R^5 and R^6 is C_{1-6}alkyl comprising a branched carbon chain.

3. 3,3-Diphenylpropylamines according to claim 1, wherein X signifies any of the following groups a)–f), each of which may carry a hydroxy substituent:



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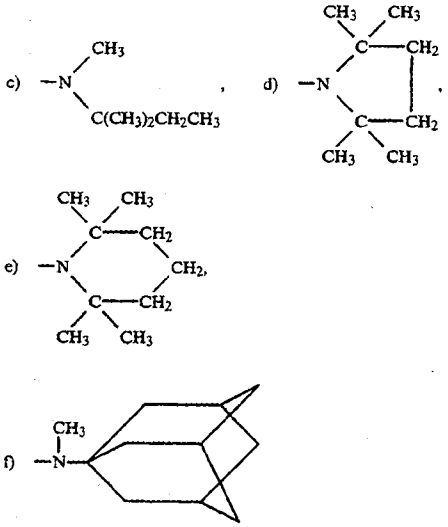


4. 3,3-Diphenylpropylamines according to claim 1, selected from the group consisting of the following compounds, their salts with physiologically acceptable acids and, where possible, their racemates and individual enantiomers: N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine,N-methyl-N-tert-.butyl-3-(2-hydroxyphenyl)-3-phenylpropylamine, N-methyl-N-tert.butyl-3-(2,4-dihydroxyphenyl)-3-phenylpropylamine, N-methyl-N-tert.butyl-3,3-bis-(2-hydroxyphenyl)propylamine, N,N-diisopropyl-3,3-bis-(2-hydroxyphenyl)propylamine, N,N-diisopropyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine, N-methyl-N-tert.butyl-3-(2,5-dihydroxyphenyl)-3-phenylpropylamine,N-N-diisopropyl-3-(2-methoxyphenyl)-3-phenylpropylamine, N-2,2,6,6-tetramethylpiperdine-,(+)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, and N,N-diisopropyl-3-(5-chloro-2-hydroxyphenyl)-3-phenylpropylamine.

5. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to claim 1 and a compatible pharmaceutical carrier.

6. The 3,3-diphenylpropylamines of claim 1 being (+)-isomers.

7. The pharmaceutical composition of claim 5 wherein the 3,3-diphenylpropylamine is present in effective anticholinergic amount.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

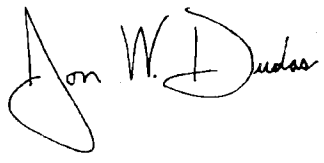
PATENT NO. : 5,382,600
APPLICATION NO. : 07/810185
DATED : January 17, 1995
INVENTOR(S) : Jönsson et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 4, col. 38, line 39:
"N-2,2,6,6-tetramethylpiperdine-" should read
--N-(3-(2-methoxyphenyl)-3-phenylpropyl)-2,2,6,6-tetramethylpiperidine--

Signed and Sealed this

Eighteenth Day of July, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT 3

US006630162B1

(12) **United States Patent**
Nilvebrant et al.

(10) **Patent No.: US 6,630,162 B1**
(45) **Date of Patent: *Oct. 7, 2003**

(54) **PHARMACEUTICAL FORMULATION AND ITS USE**

(75) Inventors: **Lisbeth Nilvebrant**, Bromma (SE); **Bengt Hallen**, Sollentuna (SE); **Birgitta Olsson**, Stenhamra (SE); **Jan Strombom**, Vattholm (SE); **Torkek Gren**, Kalamazoo, MI (US); **Anders Ringberg**, Stockholm (SE); **Martin Wikberg**, Kullavik (SE)

(73) Assignee: **Pharmacia AB**, Stockholm (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/708,428**

(22) Filed: **Nov. 9, 2000**

Related U.S. Application Data

(63) Continuation-in-part of application No. PCT/SE99/02052, filed on Nov. 11, 1999.
(60) Provisional application No. 60/202,862, filed on May 10, 2000.

(30) **Foreign Application Priority Data**

Mar. 9, 2000 (SE) 0000782

(51) **Int. Cl.**[7] **A61K 9/52**; A61K 9/54; A61K 9/26; A61K 9/16; A61K 9/22

(52) **U.S. Cl.** **424/458**; 424/457; 424/459; 424/461; 424/462; 424/468; 424/469; 424/490; 424/493; 424/494; 424/495

(58) **Field of Search** 424/457, 458, 424/459, 461, 462, 468, 469, 490, 493, 494, 495

(56) **References Cited**

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5,559,269	A	9/1996	Johansson et al.

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WO	WO9612477		5/1996
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WO	WO 98/03067	*	1/1998
WO	WO9803067		1/1998
WO	WO9811888		3/1998
WO	WO0012069		3/2000
WO	WO0027364		5/2000

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Nilvebrant et al., *Euro. J. Pharmacology*, vol. 327 (1997) pp. 195–207.
Brynne et al., *Int'l J. Clin. Pharmacology and Therapeutics*, vol. 35, No. 7 (1997) pp. 287–295.
Nilvebrant et al., *Life Sciences*, vol. 60, Nos. 13/14 (1997) pp. 1129–1136.
Stahl et al., *Neurourology and Urodynamics*, vol. 14, (1995) pp. 647–655.

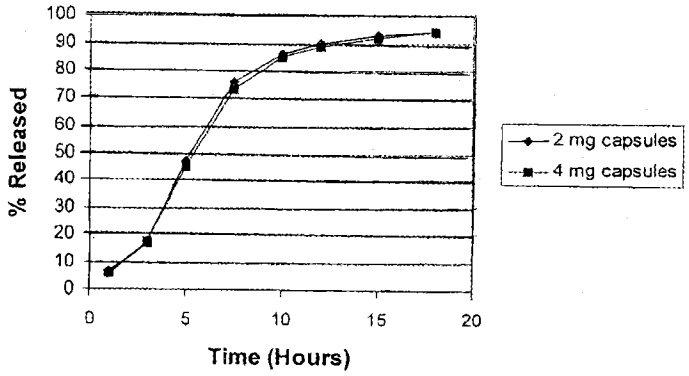
* cited by examiner

Primary Examiner—Thurman K. Page
Assistant Examiner—Todd D Ware
(74) *Attorney, Agent, or Firm*—Craig M. Bell

(57) **ABSTRACT**

The invention relates to a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours. The invention also relates to the use of the pharmaceutical formulation for treating overactive bladder and gastrointestinal disorders.

23 Claims, 1 Drawing Sheet



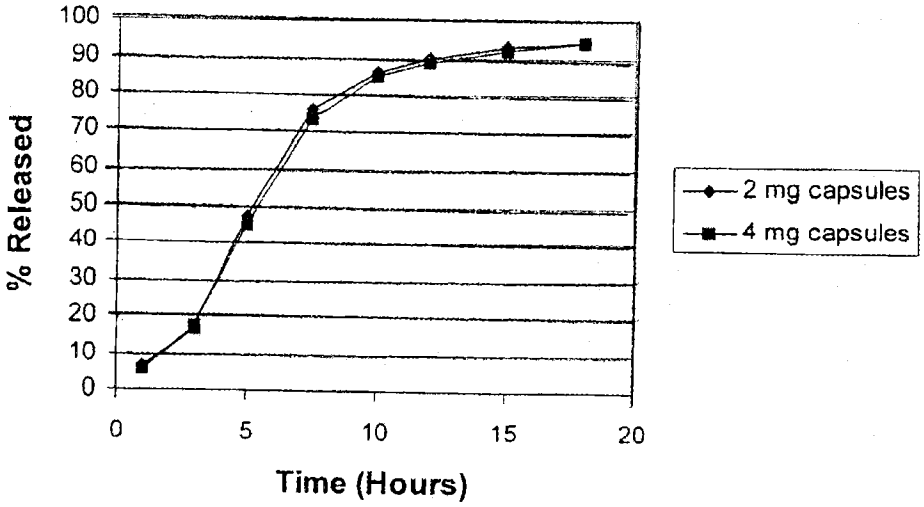

100
90
80
70
60
50
40
30
20
10
0
% Released
0
5
10
15
20
Time (Hours)
2 mg capsules
4 mg capsules

FIG. 1

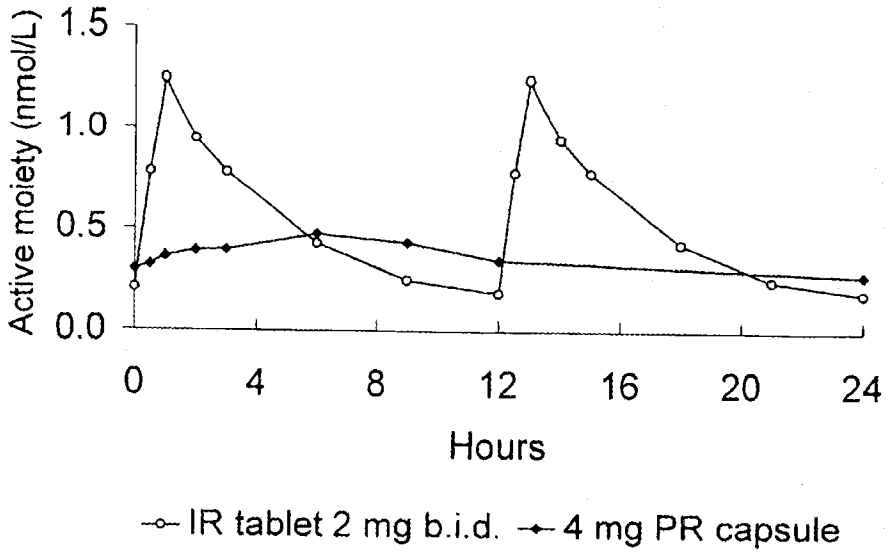

1.5
1.0
0.5
0.0
Active moiety (nmol/L)
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

PHARMACEUTICAL FORMULATION AND ITS USE

This application is a continuation-in-part of PCT international application No. PCT/SE99/02052 which has an international filing date of Nov. 11, 1999 and which designated the United States, the entire contents of which are hereby incorporated by reference. This application also claims priority under 35 U.S.C. 119(e) of U.S. Provisional No. 60/202,862, filed on May 10, 2000, the entire contents of which are also hereby incorporated by reference.

The present invention relates to a pharmaceutical formulation for administering tolterodine or a tolterodine-related compound, and to the medical use of such a formulation.

A substantial part (5–10%) of the adult population suffers from overactive or unstable urinary bladder, often also referred to as urinary incontinence. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. The prevalence of overactive bladder, particularly of so-called urge incontinence, increases with age. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Recently, however, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195–207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647–655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287–295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

Our co-pending international application PCT/SE99/01463 relates to the administration of tolterodine and tolterodine-related compounds through a controlled release formulation and is based on the finding that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

Our above-mentioned PCT/SE99/01463 discloses treatment of overactive bladder by the administration of a controlled release formulation that delivers tolterodine, a tolterodine-related compound, or a pharmacologically acceptable salt thereof such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours.

The present invention is based on the unexpected observation that a substantially constant serum level of the active moiety or moieties for 24 hours may be obtained through oral administration of a controlled release pharmaceutical formulation that releases the major content of active compound in less than about 18 hours, and more particularly that the formulation has an in vitro release of not less than about 80% after 18 hours at the conditions specified below.

In one aspect, the present invention therefore provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, as active ingredient, in which the formulation exhibits a controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours.

A second aspect of the invention relates to the use of the pharmaceutical formulation for treating a disorder or disease selected from overactive bladder (including i.a. urinary incontinence and nocturia) and gastrointestinal disorders.

A third aspect of the invention relates to the use of tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, for the preparation of the pharmaceutical formulation of the above first aspect of the invention.

Preferably, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released is not less than about 80% after 15 hours, especially not less than about 80% after 12 hours.

On the other hand, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after 1 hour is preferably not more than about 50%, especially not more than about 30%.

The fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro after three hours is preferably from about 30 to 95%, especially from about 40 to about 85%.

It may be preferred that after 7 hours, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 50%, especially not less than about 80%.

In an exemplary in vitro release profile for the pharmaceutical formulation, the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50% after 1 hour, from about 30 to about 95% after 3 hours, and more than about 50% after 7 hours.

The in vitro release measurement conditions referred to above are those for a drug release test that utilizes the United

States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deareated phosphate buffer at pH 6.8 and 37° C., where the phosphate buffer solution is prepared as described on pages 2049–2050 in USP 23. The phosphate buffer nominally contains 0.05 M phosphate.

By the term "active moiety or moities" it is meant, in the case of tolterodine and its related compounds, the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the serum profile after administration of the controlled release formulation does essentially not exhibit any substantial peak values. This may also be expressed mathematically by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI=(Cmax-Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve), and τ is the length of the dosage interval during the time τ. The controlled release formulation according to the present invention readily permits a mean fluctuation index (for n being at least 30) that is not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average unbound (blood) serum or plasma levels of active moiety (tolerodine plus metabolite) are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

The formulation of the present invention is not restricted to any particular type of formulation. Thus, various types of controlled or sustained release type formufations may be used for embodying the present invention, such as, for example, osmotic tablets, gel matrix tablets, coated beads, etc.

A common type of controlled release formulation that may be used for the purposes of the present invention comprises an inert core, such as a sugar sphere, coated with an inner drug-containing layer and an outer membrane layer controlling drug release from the inner layer. A "sealcoat" may be provided between the inert core and the layer containing the active ingredient. When the core is of a water-soluble or water-swellable inert material, the sealcoat is preferably in the form of a relatively thick layer of a water-insoluble polymer. Such a controlled release bead may thus comprise:

(i) a core unit of a substantially water-soluble or water-swellable inert material;

(ii) a first layer on the core unit of a substantially water-insoluble polymer;

(iii) a second layer covering the first layer and containing an active ingredient; and

(iv) a third layer on the second layer of polymer effective for controlled release of the active ingredient,

wherein the first layer is adapted to control water penetration into the core.

The term "control water penetration into the core" as used above means that the water influx to the core should be retarded in a controlled manner to such an extent that the drug release profile will be altered in a predictable fashion. Thus, while in many cases it may be preferred that the water penetration into the core is substantially or completely eliminated, a certain, controlled influx of water to the core may be acceptable in other cases.

The above-mentioned first layer of water-insoluble material may also serve to provide mechanical integrity to the core.

Optionally, the above-mentioned third, or controlled release layer is coated with one or more additional layers of water-soluble or insoluble polymer, e.g. a non-thermoplastic soluble polymer to decrease tackiness of the beads for subsequent processing, such as curing and filling into capsules, or a secondary functional coating, such as an enteric coating that delays the onset of drug release. Optionally, such an additional layer may contain drug for immediate release.

Usually, the first layer (ii) above constitutes more than about 2% (w/w) of the final bead composition, preferably more than about 3% (w/w), e.g. from about 3% to about 80% (w/w).

The amount of the second layer (ii) above usually constitutes from about 0.05 to about 60% (w/w), preferably from about 0.1 to about 30% (w/w) of the final bead composition.

The amount of the third layer (iv) above usually constitutes from about 1 to about 50% (w/w), preferably from about 2 to about 25% (w/w) of the final bead composition.

The core unit typically has a size in the range of from about 0.05 to about 2 mm.

The controlled release beads may be provided in a multiple unit formulation, such as a capsule or a tablet.

The cores are preferably of a water-soluble or swellable material, and may be any such material that is conventionally used as cores or any other pharmaceutically acceptable water-soluble or water-swellable material made into beads or pellets. The cores may be spheres of materials such as sucrose/starch (Sugar Spheres NF), sucrose crystals, or extruded and dried spheres typically comprised of excipients such as microcrystalline cellulose and lactose.

The substantially water-insoluble material in the first, or sealcoat layer is generally a "GI insoluble" or "GI partially insoluble" film forming polymer (dispersed or dissolved in a solvent). As examples may be mentioned ethyl cellulose, cellulose acetate, cellulose acetate butyrate, polymethacrylates such as ethyl acrylate/methyl methacrylate copolymer (Eudragit NE-30-D) and ammonio methacrylate copolymer types A and B (Eudragit RL30D and RS30D), and silicone elastomers. Usually, a plasticizer is used together with the

polymer. Exemplary plasticizers include: dibutylsebacate, propylene glycol, triethylcitrate, tributylcitrate, castor oil, acetylated monoglycerides, acetyl triethylcitrate, acetyl butylcitrate, diethyl phthalate, dibutyl phthalate, triacetin, fractionated coconut oil (medium-chain triglycerides).

The second layer containing the active ingredient may be comprised of the active ingredient (drug) with or without a polymer as a binder. The binder, when used, is usually hydrophilic but may be water-soluble or water-insoluble. Exemplary polymers to be used in the second layer containing the active drug are hydrophilic polymers such as polyvinylpyrrolidone (PVP), polyalkylene glycol such as polyethylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, or any other pharmaceutically acceptable polymer.

The ratio of drug to hydrophilic polymer in the second layer is usually in the range of from 1:100 to 100:1 (w/w).

Suitable polymers for use in the third layer, or membrane, for controlling the drug release may be selected from water-insoluble polymers or polymers with pH-dependent solubility, such as, for example, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate, polymethacrylates, or mixtures thereof, optionally combined with plasticizers, such as those mentioned above. Optionally, the controlled release layer comprises, in addition to the polymers above, another substance(s) with different solubility characteristics, to adjust the permeability, and thereby the release rate, of the controlled release layer. Exemplary polymers that may be used as a modifier together with, for example, ethyl cellulose include: HPMC, hydroxyethyl cellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone (PVP), polyvinyl alcohol, polymers with pH-dependent solubility, such as cellulose acetate phthalate or ammonio methacrylate copolymer and methacrylic acid copolymer, or mixtures thereof. Additives such as sucrose, lactose and pharmaceutical grade surfactants may also be included in the controlled release layer, if desired.

The above controlled release beads and formulation, respectively may be produced by a method comprising the following steps:

a) providing a core unit of a substantially water-soluble or water-swellable material;

b) applying a first layer of a substantially water-insoluble polymer to said core;

c) applying onto said first layer, a second layer comprising an active ingredient and optionally a polymer binder; and

d) applying onto said second layer, a third polymer layer effective for controlled release of the active ingredient; wherein the amount of material in said first layer is selected to provide a layer thickness that permits control of water penetration into the core.

Optionally, one or more additional polymer layers are applied to the core as has been mentioned above.

The preparation of the multiple unit formulation comprises the additional step of transforming the prepared beads into a pharmaceutical formulation, such as by filling a predetermined amount of the beads into a capsule, or compressing the beads into tablets.

The layering or coating operations are preferably performed by spraying a solution or dispersion of the respective layer materials onto the core, preferably in a fluid bed coating apparatus.

After the final coating step, the beads are optionally "cured", usually in a fluid bed system or in a tray dryer system, by heating to a temperature of about 30–80° C., for 30 to 180 minutes, for example. Suitably, the beads are then cooled below about 35° C. before stopping the process.

As mentioned above, the pharmaceutical formulation according to the present invention may be used for treating, inter alia, urinary disorders including overactive urinary bladder. The overactive bladder condition gives rise to urinary frequency, urgency and/or urge incontinence. Overactive bladder disorders also include nocturia, i.e. awakening at night to urinate. While overactive bladder is often associated with detrusor muscle instability, disorders of bladder function may also be due to neuropathy of the central nervous system (detrusor hyperreflexia) including spinal cord and brain lesions, such as multiple sclerosis and stroke. Overactive bladder symptoms may also result from, for example, male bladder outlet obstruction (usually due to prostatic hypertrophy), interstitial cystitis, local edema and irritation due to focal bladder cancer, radiation cystitis due to radiotherapy to the pelvis, and cystitis. The formulation may also be useful for treating gastrointestinal disorders, including gastrointestinal hyperactivity.

The pharmaceutical formulation according to the present invention has proved to be very suitable for administering the above-mentioned drug tolterodine, the chemical name of which is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, and would likewise be suitable for its related compounds, i.e. the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms and pharmacologically acceptable salts thereof.

Tolterodine is marketed for the treatment of unstable or overactive urinary bladder with symptoms including urinary incontinence (urge incontinence), urgency and urinary frequency. The 5-hydroxymethyl metabolite of tolterodine mentioned above contributes significantly to the therapeutic effect of tolterodine.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. the above-mentioned U.S. Pat. No. 5,382,600. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to the above-mentioned U.S. Pat. No. 5,559,269. The (S)-enantiomer, its non-cholinergic spasmolytic activity and use in the treatment of urinary and gastrointestinal disorders are described in WO 98/03067.

The invention will now be described in more detail by the following non-limiting Examples. Reference will be made to the accompanying drawings, wherein:

FIG. 1 is a diagram showing the fraction of tolterodine L-tartrate released in vitro versus time for 2 and 4 mg controlled release capsules according to the Example below; and

FIG. 2 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a prede-

termined total dosage of tolterodine (4 mg) through a prolonged release (PR) capsule (4 mg) according to the Example below once daily. The corresponding variation with a prior art immediate release (IR) tablet (2 mg) twice daily is also shown.

EXAMPLE

Preparation of Controlled Release Beads and Capsules

An exemplary bead formulation containing tolterodine L-tartrate as active ingredient has the following structure:

Core:	Starch-containing sugar sphere of about 0.8 mm diameter (commercially available); comprises 73% w/w of the final bead; purpose: coating substrate;
First layer:	Surelease ® "sealcoat" (Surelease ® is an aqueous film-coating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil, and manufactured by Colorcon, Inc, USA); comprises about 12% w/w of the final bead; purpose: to provide more consistent core surface; during drug release phase maximize time that drug is saturated inside bead and minimize osmotic effects; control drug release rate together with the third layer;
Second layer:	Tolterodine L-tartrate/hydroxypropylmethylcellulose (HPMC); comprises about 3% w/w of the final bead; ratio of Tolterodine:HPMC is 5:1; purpose: drug supply;
Third layer:	Surelease ®/HPMC; comprises about 12% w/w of the final bead; ratio of Surelease ®:HPMC is 6:1; purpose: drug release rate control;

Beads with a three-layer coating having the above characteristics were prepared as follows:

1200 g of sugar spheres, 20–25 mesh, were charged into a Wurster fluid bed and sequentially coated at a nominal product temperature of 36 to 40° C. with the following three coating liquids:

(1) a Surelease® sealcoating liquid prepared by mixing 788 g of Surelease® with 563 g of purified water;

(2) a drug-containing solution prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of hydroxypropylmethyl cellulose (HPMC) 5 cP; and

(3) a sustained release coating liquid prepared by mixing 29 g of HPMC 5 cP with 375 g of purified water, and then mixing with 695 g of Surelease®.

After tray drying for 3 hours at 70° C., the coated spheres were filled into size #4 or size #3 hard gelatin capsules to obtain 2 mg and 4 mg tolterodine L-tartrate capsules, respectively, of the composition:

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20–25 mesh	68.6 mg	137.2 mg
Surelease ®	21.2 mg	42.4 mg
HPMC 5cP	2.0 mg	4.0 mg

Optionally, a fourth layer may be applied to the bead before drying by Wurster coating.

Fourth layer:	HPMC; comprises about 1% w/w of the final bead; purpose: decrease tackiness of beads for subsequent processing (curing and capsule filling).

In the case of the above described bead, such a fourth layer may be applied with a coating solution prepared by dissolving 16.4 g of HPMC in 234 g of water.

Drug In Vitro Release Study

A drug-release test which utilizes the USP Apparatus 1 (rotating basket) at 100 rpm with 1000 mL of deaerated phosphate buffer prepared at pH 6.8, was used to study the in vitro release at 37° C. of the two three-layered beads-containing 2 and 4 mg capsules prepared above. The buffer was identical to that used for the Buffer Stage testing of Delayed-release dosage forms described in USP 23 General Chapter 724, and nominally contains 0.05 M phosphate and 0.075 M chloride. The results are shown in FIG. **1**. As can be seen therein, about 90% of the tolterodine tartrate had been released from both capsules after 12 hours.

Pharmacokinetic Study—Determination of Serum Concentrations of Tolterodine and Main Metabolite

A clinical trial was performed in patients with overactive bladder to determine the pharmacokinetic effects of a (i) a once daily dose of a 4 mg tolterodine controlled release capsule (below referred to as TOD) as described above, and (ii) two doses daily of a tolterodine immediate release tablet (below referred to as TIR), described below. 30 patients were subjected to each of the treatments. The measurements were performed on day seven in each treatment period and included measurements of serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time.

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human 25 serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136). FIG. **2** shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily (PR capsule in FIG. **2**), and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as FI=(Cmax—Cmin)/AUCτ/τ, where τ is the length of the dosage interval and AUCτ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index

for the active moiety was 2.29 (95% CI 1.95–2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59–0.78) for the TOD capsule.

While the invention has been described above with reference to specific embodiments thereof, it is not restricted thereto in any way whatsoever. On the contrary, as will be understood by those skilled in the art, various changes, modifications, substitutions and omissions can be made without departing from the basic concept of the invention as defined in the claims which follow. Thus, for example, other sustained release formulations may be used.

What is claimed is:

1. An oral pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, as active ingredient, wherein said formulation exhibits controlled in vitro release of the active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours, and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours, and wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as $FI=(Cmax-Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

2. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80% after 15 hours.

3. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not less than about 80% after 12 hours.

4. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 50% after 1 hour.

5. The formulation according to claim 4, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is less than about 30% after 1 hour.

6. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 30 to about 95% after 3 hours.

7. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is from about 40 to about 85% after 3 hours.

8. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 50% after 7 hours.

9. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is more than about 80% after 7 hours.

10. The formulation according to claim 1, wherein the fraction of tolterodine, tolterodine-related compound or salt thereof that is released in vitro is not more than about 50% after 1 hour, from about 30 to about 95% after 3 hours, and not less than about 50% after 7 hours.

11. The formulation according to claim 1, wherein the in vitro release is measured by a drug release test which utilizes the United States Pharmacopea (USP) Apparatus 1 (rotating basket) at 100 rpm with 900 ml of deaerated phosphate buffer at pH 6.8 and 37° C., where the phosphate buffer solution is prepared as described on pages 2049–2050 of USP 23, and nominally contains 0.05 M phosphate.

12. The formulation according to claim 1, which comprises tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a salt thereof.

13. The formulation according to claim 1, which comprises tolterodine, or a salt thereof.

14. The formulation according to claim 1, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

15. The formulation according to claim 14, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

16. A method of treating an overactive bladder, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

17. A method of treating urinary incontinence, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

18. A method of treating nocturia, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

19. A method of treating gastrointestinal disorders, which comprises administering a therapeutically effective amount of a pharmaceutical formulation according to claim 1.

20. A method for orally administering tolterodine or a tolterodine-related compound, or a pharmacologically acceptable salt thereof, to a patient to maintain a substantially constant serum level of the active moiety or moieties for 24 hours, which method comprises administering a pharmaceutical formulation containing tolterodine, a tolterodine-related compound or a salt thereof, which formulation exhibits a controlled in vitro release in phosphate buffer at pH 6.8 of tolterodine, tolterodine-related compound or salt thereof of not less than about 80% after 18 hours.

21. The formulation according to claim 1, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

22. The formulation according to claim 15, wherein the 24-hour serum profile, is from about 10 nM*h to about 120 nM*h.

23. The formulation according to claim 16, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

* * * * *

EXHIBIT 4

US006770295B1

(12) **United States Patent**
Kreilgård et al.

(10) **Patent No.: US 6,770,295 B1**
(45) **Date of Patent: Aug. 3, 2004**

(54) **THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/582,498**

(22) PCT Filed: **Aug. 26, 1999**

(86) PCT No.: **PCT/SE99/01463**

§ 371 (c)(1),
(2), (4) Date: **Nov. 14, 2000**

(87) PCT Pub. No.: **WO00/12069**

PCT Pub. Date: **Mar. 9, 2000**

(30) **Foreign Application Priority Data**

Aug. 27, 1998 (SE) 9802864
Nov. 11, 1998 (SE) 9803871

(51) **Int. Cl.**[7] **A61K 9/22**; A61K 9/52; A61K 9/70; A61F 13/00

(52) **U.S. Cl.** **424/457**; 424/468; 424/449

(58) **Field of Search** 424/449, 457, 424/468, 458, 459, 461, 462

(56) **References Cited**

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WO	WO9811888	3/1998

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Stahl, M.M.S., Neurology and Urodynamics, vol. 14 (1995) pp. 647–655.
Nilsson, C.G. et al., Neurology and Urodynamics, vol. 16 (1997) pp. 533–542.

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(57) **ABSTRACT**

The present invention is drawn to a method of treating an unstable or overactive urinary bladder by treating the patient with tolterodine or a tolterodine-related compound, or pharmaceutically acceptable salt thereof, with a controlled release formulation that maintains a substantially constant serum level of the active moiety or moieties for at least 24 hours. The present invention is further drawn to a formulation for the method.

27 Claims, 2 Drawing Sheets

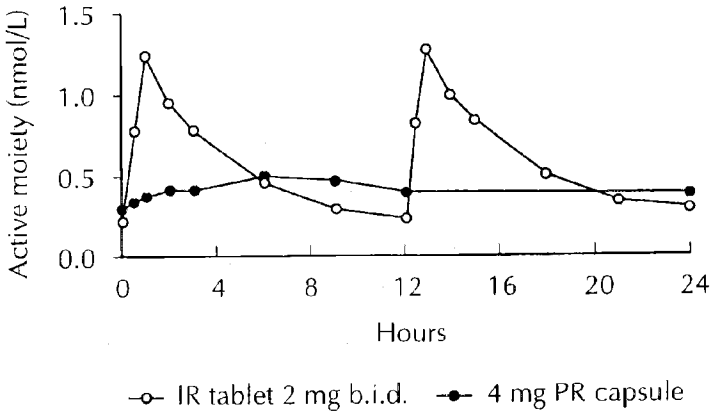


FIG. 1

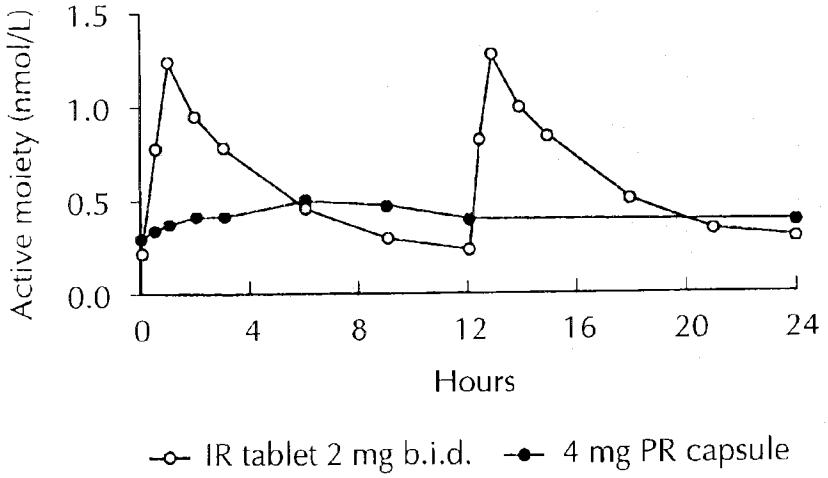

Active moiety (nmol/L)
1.5
1.0
0.5
0.0
0
4
8
12
16
20
24
Hours
IR tablet 2 mg b.i.d.
4 mg PR capsule

FIG. 2

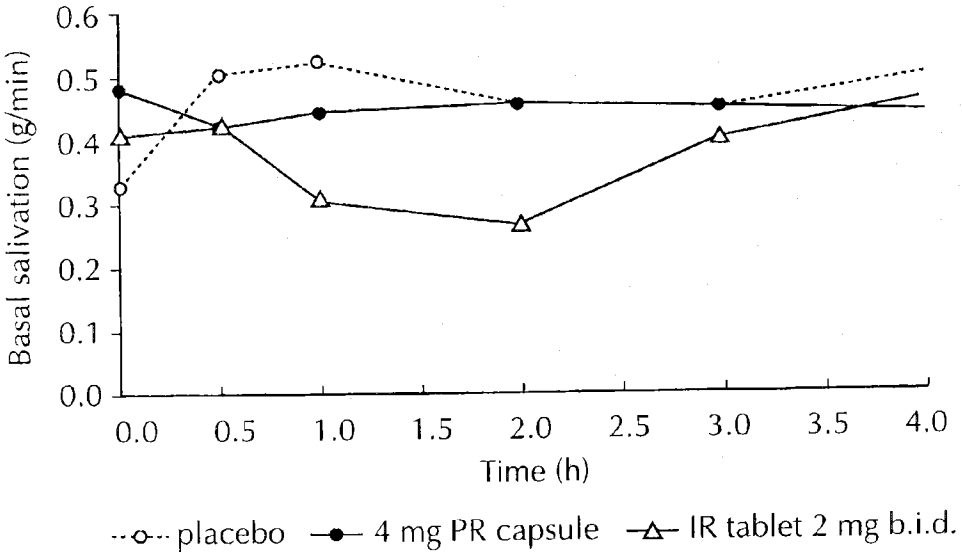
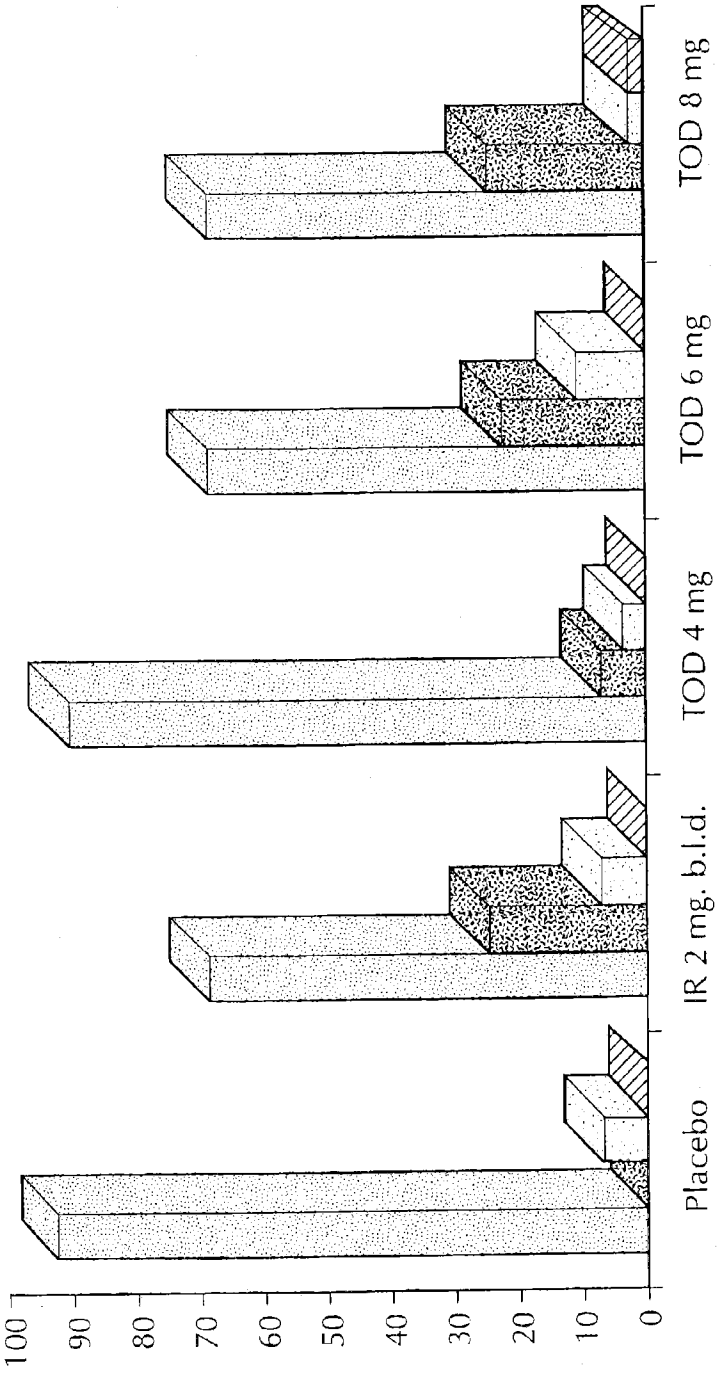

Basal salivation (g/min)
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (h)
placebo
4 mg PR capsule
IR tablet 2 mg b.i.d.

FIG. 3


100
90
80
70
60
50
40
30
20
10
0
Placebo
IR 2 mg. b.l.d.
TOD 4 mg
TOD 6 mg
TOD 8 mg

THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

This application is the national phase under 35 U.S.C. §371 of PCT International Application No. PCT/SE99/01463 which has an International filing date of Aug. 26, 1999, which designated the United States of America.

The present invention relates to an improved method of treating unstable or overactive urinary bladder as well as a formulation therefor.

A substantial part (5–10%) of the adult population suffers from urinary incontinence, and the prevalence, particularly of so-called urge incontinence, increases with age. The symptoms of an unstable or overactive bladder comprise urge incontinence, urgency and urinary frequency. It is assumed that unstable or overactive bladder is caused by uncontrolled contractions of the bundles of smooth muscle fibres forming the muscular coat of the urinary bladder (the detrusor muscle) during the filling phase of the bladder. These contractions are mainly controlled by cholinergic muscarinic receptors, and the pharmacological treatment of unstable or overactive bladder has been based on muscarinic receptor antagonists. The drug of choice has for a long time been oxybutynin.

Oxybutynin, which chemically is the DL-racemic form of 4-diethylamino-2-butynyl-phenylcyclohexylglycolate, is given orally, usually as a tablet or syrup. Oxybutynin, usually administered as the chloride salt, is metabolized to an active metabolite, N-desethyl-oxybutynin. The drug is rapidly absorbed from the gastrointestinal tract following administration and has a duration of from three to six hours. While the effectiveness of oxybutynin has been well documented, its usefulness is limited by classical antimuscarinic side-effects, particularly dry mouth, which often leads to discontinuation of treatment.

WO 96/12477 discloses a controlled release delivery system for oxybutynin, which delivery system is said not only to be of convenience to the patient by reducing the administration to a once daily regimen, but also to reduce adverse side-effects by limiting the initial peak concentrations of oxybutynin and active metabolite in the blood of the patient.

The alleged relief of side-effects by reducing or eliminating peak concentrations through administration of the controlled release delivery system is, however, contradicted by a later published clinical report, Nilsson, C. G., et al., Neurourology and Urodynamics 16 (1997) 533–542, which describes clinical tests performed with the controlled release delivery system disclosed in WO 96/12477 above. In the clinical tests reported, a 10 mg controlled release oxybutynin tablet was compared with the administration of a conventional (immediate release) 5 mg tablet given twice daily to urge incontinent patients. While high peak levels of the drug obviously were eliminated with the controlled release oxybutynin tablet, no difference in side-effects between the controlled release tablet and the conventional tablet was observed. The advantage of the controlled release tablet thus resided merely in enhancing treatment compliance by its once-a-day dosage rather than also reducing side-effects as stated in WO 96/12477.

Recently, an improved muscarinic receptor antagonist, tolterodine, (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine, has been marketed for the treatment of urge incontinence and other symptoms of unstable or overactive urinary bladder. Both tolterodine and its major, active metabolite, the 5-hydroxymethyl derivative of tolterodine, which significantly contributes to the therapeutic effect, have considerably less side-effects than oxybutynin, especially regarding the propensity to cause dry mouth. While tolterodine is equipotent with oxybutynin in the bladder, its affinity for muscarinic receptors of the salivary gland is eight times lower than that of oxybutynin; see, for example, Nilvebrant, L., et al., European Journal of Pharmacology 327 (1997) 195–207. The selective effect of tolterodine in humans is described in Stahl, M. M. S., et al., Neurourology and Urodynamics 14 (1995) 647–655, and Bryne, N., International Journal of Clinical Pharmacology and Therapeutics, Vol. 35, No. 7 (1995) 287–295.

The currently marketed administration form of tolterodine is filmcoated tablets containing 1 mg or 2 mg of tolterodine L-tartrate for immediate release in the gastrointestinal tract, the recommended dosage usually being 2 mg twice a day. While, as mentioned, the side-effects, such as dry mouth, are much lower than for oxybutynin, they still exist, especially at higher dosages.

According to the present invention it has now surprisingly been found that, contrary to the case of oxybutynin, the substantial elimination of peak serum levels of tolterodine and its active metabolite through controlled release of tolterodine for an extended period of time, such as through a once-daily administration form, while maintaining the desired effect on the bladder, indeed gives a significant reduction of the (already low) side-effects, particularly dry mouth, compared with those obtained for the same total dosage of immediate release tablets over the same period. In other words, eliminating the peak serum levels of the active moiety affects the adverse effects, and particularly dry mouth, more than the desired effect on the detrusor activity, simultaneously as the flattening of the serum concentration does not lead to loss of activity or increased incidence of urinary retention or other safety concerns. Thus, in addition to the convenience advantage of controlled release administration, one may either (i) for a given total dosage of tolterodine, reduce the side-effects, such as dry mouth, or (ii) for a given level of acceptable side-effects, increase the dosage of tolterodine to obtain an increased effect on the bladder, if desired.

In one aspect, the present invention therefore provides a method of treating unstable or overactive urinary bladder, which method comprises administering to a (mammal) patient in need of such treatment tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, through a controlled release formulation that administers tolterodine or said tolterodine-related compound, or salt thereof, at a controlled rate for at least 24 hours. It is preferred that the dosage form formulation is capable of maintaining a substantially constant serum level of the active moiety or moieties for said at least 24 hours.

Overactive urinary bladder encompasses detrusor instability, detrusor hyperreflexia, urge incontinence, urgency and urinary frequency.

As mentioned above, the chemical name of tolterodine is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine. The term "tolterodine-related compound" is meant to encompass the major, active metabolite of tolterodine, i.e. (R)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; the corresponding (S)-enantiomer to tolterodine, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; the 5-hydroxymethyl metabolite of the (S)-enantiomer, i.e. (S)-N,N-diisopropyl-3-(2-hydroxy-5-hydroxymethylphenyl)-3-phenylpropanamine; as well as the corresponding racemate to tolterodine, i.e. (R,S)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine; and prodrug forms thereof.

By the term "active moiety or moities" is meant the sum of free or unbound (i.e. not protein bound) concentrations of (i) tolterodine and active metabolite thereof, when tolterodine (or prodrug form) is administered; or (ii) tolterodine and active metabolite thereof and/or (S)-enantiomer to

tolterodine and active metabolite thereof, when the corresponding racemate (or prodrug form) is administered; or (iii) active metabolite, when the (R)-5-hydroxymethyl metabolite of tolterodine (or prodrug form) is administered; or (iv) (S)-enantiomer to tolterodine and active metabolite thereof, when the (S)-enantiomer (or prodrug) is administered; or (v) active (S)-metabolite, when the (S)-5-hydroxymethyl metabolite is administered.

The term "substantially constant" with respect to the serum level of active moiety or moieties means that the release profile of the controlled release formulation should essentially not exhibit any peak values. This may, more sophistically, also be expressed by reference to the "fluctuation index" (FI) for the serum concentration of (unbound) active moiety (or sum of active moities when relevant), where the fluctuation index FI is calculated as

$$FI=(Cmax-Cmin)/AUC\tau/\tau$$

wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety, AUCτ is the area under the serum concentration profile (concentration vs time curve) for dosage interval τ, and τ is the length of the dosage interval. Thus, according to the present invention, the controlled release formulation should provide a mean fluctuation index (for n being at least 30) that is usually not higher than about 2.0, more preferably not higher than about 1.5, particularly not higher than about 1.0, for example not higher than about 0.8.

For tolterodine and its 5-hydroxymethyl metabolite, the 24-hour exposure, expressed as AUC unbound active moiety (tolterodine plus metabolite) is usually in the range of from about 5 to about 150 nM*h, preferably from about 10 to about 120 nM*h, depending on the dosage needed by the particular patient. The indicated limits are based upon calculation of the unbound concentrations of active moiety assuming a fraction unbound of 3.7% for tolterodine and 36% for the 5-hydroxymethyl metabolite (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136).

Correspondingly, for tolterodine and its 5-hydroxymethyl metabolite, the average (blood) serum or plasma levels are usually in the range of about 0.2 to about 6.3 nM, preferably in the range of about 0.4 to about 5.0 nM.

Tolterodine, its corresponding (S)-enantiomer and racemate and the preparation thereof are described in e.g. WO 89/06644. For a description of the active (R)-5-hydroxymethyl metabolite of tolterodine (as well as the (S)-5-hydroxymethyl metabolite), it may be referred to WO 94/11337. The (S)-enantiomer and its use in the treatment of urinary and gastrointestinal disorders is described in WO 98/03067.

In another aspect, the present invention provides a pharmaceutical formulation containing tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine or said tolterodine-related compound, or salt thereof, for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

Still another aspect of the present invention provides the use of tolterodine or a tolterodine-related compound, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation provides a controlled release of tolterodine or said tolterodine-related compound, or salt thereof at a controlled rate for at least 24 hours, preferably such that a substantially constant serum level of the active moiety or moieties is maintained for said at least 24 hours.

The controlled release formulation is preferably an oral delivery system or a transdermal preparation, such as a transdermal patch, but also other controlled release forms may, of course, be contemplated, such as buccal tablets, rectal suppositories, subcutaneous implants, formulations for intramuscular administration.

An exemplary type of oral controlled release formulation, a specific embodiment of which is described in Example 1 below, is a multi-unit formulation comprising controlled-release beads. Each bead comprises (i) a core unit of a water-soluble, water-swellable or water-insoluble inert material (having a size of about 0.05 to 2 about 2 mm), such as e.g. a sucrose sphere; (ii) a first layer on the core of a substantially water-insoluble (often hydrophilic) polymer (this layer may be omitted in the case of an insoluble core, such as e.g. of silicon dioxide), (iii) a second layer of a water-soluble polymer having an active ingredient dissolved or dispersed therein, and (iv) a third polymer layer effective for controlled release of the active ingredient (e.g. a water-insoluble polymer in combination with a water-soluble polymer) In the case of an oral controlled release formulation for once-daily administration, the dosage of tolterodine (or tolterodine related compound) is, for example, 4 mg or 6 mg.

A transdermal patch for tolterodine or tolterodine-related compound is described in our co-pending international application "Transdermally administered tolterodine as antimuscarinic agent for the treatment of overactive bladder" (based on Swedish patent application no. 9802864-0, filed on Aug. 27, 1998), the full disclosure of which is incorporated by reference herein. Illustrative patch formulations are described in Example 2 below.

With the guidance of the disclosure herein, the skilled person may either adapt controlled release administration forms, such as tablets, capsules, patches etc, known in the art, to obtain the objectives of the present invention, or design modified or new controlled release administration forms.

The invention is illustrated by the following Examples, without, however, limiting the scope of the invention in any way. Percentages are by weight, unless otherwise stated. Reference will be made to the accompnaying drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagram showing the variation of serum concentration (nmol/L) of (unbound) active moiety with time (hours) during 24 hours when administering a predetermined total dosage of tolterodine (4 mg) through (i) an immediate release tablet (2 mg) twice daily as in the prior art, and (ii) a controlled release capsule (4 mg) once daily in accordance with the present invention;

FIG. 2 is a diagram showing the variation of the basal salivation (9/min) with time (hours) during 4 hours after administration of (i) a 4 mg tolterodine controlled release capsule in accordance with the present invention, (ii) a prior art tolterodine immediate release tablet, and (iii) placebo; and

FIG. 3 is is a bar chart diagram showing patients' individual estimates of experienced dry mouth side effect (no dry mouth, mild, moderate, severe) after administration of tolterodine through (i) a conventional 2 mg immediate release tablet, (ii) controlled release capsules of 4, 6 and 8 mg, respectively, according to the present invention, and (iii) placebo.

EXAMPLE 1

TOLTERODINE ORAL CR CAPSULE AND IR TABLET

Preparation of Tolterodine CR Capsules 2 mg and 4 mg

A controlled release (CR) capsule containing non-pareil beads coated by (i) an ethylcellulose layer, (ii) a tolterodine/

HPMC layer, and (iii) a sustained release ethylcellulose/HPMC layer was prepared as follows:

1200 g of (starch-containing) sugar spheres, 20–25 mesh, were charged into a Wurster fluid bed and sequentially coated with the following three coating solutions:

(1) a Surelease® sealcoating solution prepared by mixing 788 g of Sureleasee with 563 g of purified water (Surelease® is an aqueous filmcoating dispersion, about 25% solids, consisting primarily of ethylcellulose plasticized with fractionated coconut oil; manufactured by Colorcon, Inc., West Point, Pa., U.S.A.);

(2) a suspension prepared by first dissolving 35.0 g of tolterodine L-tartrate in 2190 g of purified water, and then mixing the solution with 6.6 g of Hypromellose, 5 cP (hydroxypropylmethyl cellulose (HPMC)); and

(3) a sustained release coating solution prepared by mixing 29 g of Hypromellose, 5 cP, with 375 g of purified water, and then mixing with 695 g of Surelease®.

After drying, the coated spheres were filled into hard gelatin capsule shells (size 3, white/white) to obtain 2 mg and 4 mg capsules, respectively, of the composition (filling mass for 2 mg capsule, 169–207 mg/capsule):

	2 mg capsule	4 mg capsule
Tolterodine L-tartrate	2.0 mg	4.0 mg
sugar spheres, 20–25 mesh	69 mg	137 mg
Surelease ®	21 mg	42 mg
Hypromellose, 5cP	2.0 mg	4.1 mg

Tolterodine L-Tartrate IR Tablets 2 mg

Commercially available tolterodine L-tartate 2 mg tablets for immediate release (IR) (Detrusitol®, Pharmacia & Upjohn AB, Sweden) were used. The tablets had the following composition:

Core	
Tolterodine L-tartrate	2.0 mg
cellulose, microcrystalline	53.4 mg
calcium hydrogen phosphate dihydrate	18.0 mg
sodium starch glycollate	6.0 mg
magnesium stearate	0.4 mg
colloidal anhydrous silica	0.2 mg
Coating	
Methylhydroxypropyl cellulose	1.5 mg
cellulose, microcrystalline	0.3 mg
stearic acid	0.6 mg
titanium dioxide E 171	0.6 mg

PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

A clinical trial was performed in patients with overactive bladder to determine the pharmacodynamic and pharmacokinetic effects of different daily doses of (i) the above described tolterodine controlled release capsule (below referred to as TOD), compared with (ii) the above described tolterodine immediate release tablet (below referred to as TIR), and (iii) a placebo capsule (containing sugar spheres only). The trial was performed as a double-blind, double dummy, cross-over trial in 60 patients for three one week periods and six treatments (2, 4, 6 and 8 mg TOD once daily, 2 mg TIR twice daily, and placebo). All patients were randomised to three out of six treatments, meaning that 30 patients were subjected to each of the treatments. Pharmacodynamic and pharmacokinetic measurements were performed on day seven in each treatment period. The determinations included measurements of (i) serum concentrations of tolterodine and its main 5-hydroxymethyl metabolite (below called 5-HM) over time, (ii) salivation (dry mouth), and (iii) residual urine volumes.

Serum Concentrations of Tolterodine and Main Metabolite

Blood samples were drawn immediately before dosing and after 0.5, 1, 2, 3, 6, 9, 12, 24 and 25 hours, and the free (unbound) serum concentrations of tolterodine and its 5-HM metabolite were measured by gas chromatography/mass spectrometry. The unbound concentrations were calculated assuming a fraction unbound of 3.7% for tolterodine and of 36% for 5-HM as obtained from protein binding studies on human serum (Nilvebrant, L., et al., Life Sciences, Vol. 60, Nos. 13/14 (1997) 1129–1136). FIG. **1** shows the obtained variation with time of the sum of the unbound concentrations of tolterodine and 5-HM (which sum is referred to as "active moiety") for, on the one hand, the administration of a 4 mg TOD capsule once daily, and, on the other hand, the administration of a 2 mg TIR tablet twice daily (i.e. equivalent 24-hour doses of capsule and tablet). As shown in the Figure, the peaks obtained with the TIR tablet are eliminated with the TOD capsule, the latter thus providing a substantially constant serum concentration of active moiety during the 24 hours illustrated.

The difference in fluctuation of the serum concentrations between TIR tablet and TOD capsule may also be demonstrated by calculation of the "fluctuation index". The fluctuation index, FI, is calculated as $FI=(Cmax-Cmin)/AUC\tau/\tau$, where τ is the length of the dosage interval and $AUC\tau$ is the area under the serum concentration profile during a dosage interval. Thus, the mean calculated fluctuation index for the active moiety was 2.40 (95% CI 1.95–2.63) for the TIR tablet (based on n=28), and 0.68 (95% CI 0.59–0.78) for the TOD capsule.

Salivation (Dry Mouth)

Salivation was measured using dental cotton rolls applied in the mouth for 3×2 minutes. Measurements were performed before breakfast and thereafter after each blood sample on day seven in each treatment period. Based on all measurements after dosing, the mean salivation during 12 hours was calculated. The basal salivation at steady state was measured after treatment with (i) 4 mg TOD capsule, (ii) 2 mg TIR tablet, and (iii) placebo. The results are presented in FIG. **2**. As can be seen in the Figure, the salivation is substantially constant during the period shown for the TOD capsule, whereas a considerable reduction in salivation (i.e. drier mouth) is obtained with the TIR tablet.

While FIG. **2** shows the total salivation as measured, the degree of salivation, or dry mouth, was also determined, based on the patient's estimate of experienced intensity of the phenomenon. The results for 2 mg TIR tablet b.i.d., 4 mg TOD capsule, 6 mg TOD capsule and 8 mg TOD capsule, are presented in bar chart form in FIG. **3**. The four bars for each dosage represent, from left to right in the figure, no dry mouth, mild, moderate, and severe, respectively.

As apparent from FIG. **2**, the dry mouth intensity for the TIR 2 mg b.i.d. tablet is clearly higher than that of the TOD 4 mg capsule, and about twice that dosage, i.e. TOD 8 mg, is required to match the adverse dry mouth effects of the TIR 2 mg b.i.d. tablet.

The results from the salivation determinations thus show that flattening of the concentration peaks of the "active

moiety" (i.e. tolterodine plus 5-HM) leads to a substantial reduction of the undesired dry mouth effect.

Residual Urine Volume

Residual volume is the volume of urine left in the bladder immediately after voiding. Measuring residual volume offers a method of assessing the effect of antimuscarinic treatment on the bladder. In fact, it offers a measure of efficacy (change in residual volume) as well as safety (urinary retention, i.e. inability to pass urine). Efficacy may thus be measured as the mean residual volume per unit of time, and safety as any case where the residual urine exceeds a fixed level. The mean residual volume per micturition was measured by a non-invasive (ultrasonic) method for placebo, TIR tablet 2 mg b.i.d., and for capsules TOD 2 mg, TOD 4 mg, TOD 6 mg, and TOD 8 mg.

The results are presented in Tables 1 and 2 below. Table 1 shows the mean residual volume per micturition, and Table 2 shows the maximum residual volume during 12 hours.

The results presented clearly demonstrate that the TOD capsule dosages are as efficacious as the corresponding TIR b.i.d dosages, and also that the TOD dose may be increased up to 8 mg daily and still be safe with regard to urinary retention.

TABLE 1

Mean Residual Volume per micturition (ml)

	Placebo	TIR 2 mg b.i.d	TOD 2 mg	TOD 4 mg	TOD 6 mg	TOD 8 mg
Estimated mean	29	62	40	59	69	77
95% confidence interval	12 to 46	45 to 79	26 to 55	51 to 66	60 to 78	65 to 89
Estimated difference vs. IR			−22	−4	7	14
			−44 to 1	−23 to 15	−13 to 26	−7 to 36

TABLE 2

Maximum Residual Volume during 12 hours

	Placebo	TIR 2 mg b.i.d	TOD 2 mg	TOD 4 mg	TOD 6 mg	TOD 8 mg
Median value (ml)	46	72	45	55	87	77
min–max	5–267	10–316	0–192	0–349	0–360	0–390

The results from the clinical trial described above demonstrate that a flatter serum concentration of active moiety (tolterodine plus 5-HM) not only does not lead to a loss of efficacy or to untoward side-effects, primarily urinary retention, but, importantly, also provides for a reduced dry mouth effect (unaffected or less reduced salivation).

EXAMPLE 2

TOLTERODINE TRANSDERMAL PATCH FORMULATION

Tolterodine-releasing patches were prepared as follows:

System 1 (Drug-in-Adhesive, Acrylate)

5 g of tolterodine base were dissolved in 11 g of ethanol and added to 20 g of Durotak 387-2287 (National Starch & Chemical, U.S.A.). The drug gel was coated onto a backing membrane (Scotchpak 1012; 3M Corp., U.S.A.) by using a coating equipment (RK Print Coat Instr. Ltd, Type KCC 202 control coater). The wet layer thickness was 400 μm. The laminate was dried for 20 min. at RT and then for 30 min. at 40° C. A polyester release liner (S 2016; Rexam Release) was laminated onto the dried drug gel. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,5 mg/cm^2.

System 2 (Multi-laminate, Acrylate)

5 g of tolterodine base were dissolved in 10 ml of ethanol. A mix of 6,4 g of Eudragit RL 100 (Röhm GmbH Chemische Fabrik, Germany) and 6,4 of ethanol and a mix of 2,6 g of Polyvidone 90 (BASF, Germany) and 10,2 g of ethanol were added to the solution of tolterodine base in ethanol. Finally, 4 g of propylene glycol were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment above. The wet layer thickness was 400 μm. The laminate was then dried at 40° C. for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80° C. for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 2,0 mg/cm^2.

System 3 (Multi-laminate Water-based Acrylate)

1 g of tolterodine base was mixed with Tween 80 (Merck) by heating to 60–70° C. 1,8 g of triethylacetate and 1,3 g of dem. water was added to the mix. The final mix was then added to 25 g of Eudragit RL 30 D (Röhm GmbH Chemische Fabrik, Germany). Finally, 180 mg of 1 N NaOH were added. The drug gel was coated onto a backing membrane (Scotchpak 1109; 3M Corp., U.S.A.) by using the coating equipment. The wet layer thickness was 400 μm. The laminate was dried at 40° C. for 2 hours. An adhesive layer consisting of Plastoid E35H was coated onto a polyester film (S 2016; Rexam Release) and dried at 80° C. for 10 min. The two layers were thereafter laminated. The sheet was cut into patches and stored at 2–8° C. until use (packed in Barex pouches). The concentration of tolterodine base in the patches was 0,5 mg/cm^2.

What is claimed is:

1. A method of treating unstable or overactive urinary bladder, wherein the method comprises administering to a patient in need of such treatment tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through a controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or moieties for at least 24 hours, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

2. The method according to claim **1**, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as FI=(Cmax−Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

3. A method of treating unstable or overactive urinary bladder, wherein the method comprise administering to a patient in need of such treatment tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, in a pharmaceutically effective amount thereof through controlled release formulation capable of maintaining a

substantially constant serum level of the active moiety or moieties for at least 24 hours with reduced undesirable side effects and with no reduction in the efficacy of the tolterodine compound, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

4. The method according to claim **1**, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

5. The method according to claim **1** wherein the controlled release formulation is a capsule or tablet for oral administration once daily.

6. The method according to claim **1**, wherein the controlled release formulation is a transdermal preparation.

7. The method according to claim **1** wherein tolterodine is administered.

8. The method according to claim **1** wherein urinary incontinence is treated.

9. A pharmaceutical formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

10. The formulation of claim **9**, which provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as $FI=(Cmax-Cmin)/AUC\tau/\tau$, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, $AUC\tau$ is the area under the serum concentration profile, and τ is the length of the dosage interval.

11. A pharmaceutical formulation containing tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of said tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine, or pharmaceutically acceptable salt thereof, such that a substantially constant serum level of the active moiety or moieties is maintained for at least 24 hours for efficacious therapy with reduced undesirable side effects, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from 5 to about 150 nM*h.

12. The formulation according to claim **9**, wherein tolterodine, its 5-hydroxymethyl metabolite or the racemate corresponding to tolterodine is administered, and the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.2 to about 6.3 nM.

13. The formulation according to claim **9**, which is a capsule or tablet for oral administration once daily.

14. The formulation according to claim **1**, which is a transdermal preparation.

15. The formulation according to claim **9**, which provides controlled release of tolterodine.

16. The method of claim **3**, wherein the controlled release formulation is administered orally.

17. The formulation of claim **11**, which is in a form for oral administration.

18. The method according to claim **2**, wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

19. The method according to claim **3**, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 10 nM*h to about 120 nM*h.

20. The method according to claim **4**, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

21. The method according to claim **6**, wherein the transdermal preparation is a transdermal patch.

22. The formulation of claim **10**, wherein the mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 1.0.

23. The formulation according to claim **11**, wherein the 24-hour serum profile, expressed as the AUC of unbound tolterodine and 5-hydroxymethyl metabolite, is from about 10 nM*h to about 120 nM*h.

24. The formulation according to claim **12**, wherein the serum level of unbound tolterodine and 5-hydroxymethyl metabolite is in the range of about 0.4 to about 5.0 nM.

25. The transdermal preparation of claim **14**, which is a transdermal patch.

26. The method of claim **3**, wherein increased efficacy of the tolterodine compound is obtained with minimal undesirable side effects.

27. The formulation of claim **11**, wherein increased efficacy of the tolterodine compound is obtained with minimal undesirable side effects.

* * * * *

EXHIBIT 5

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(973) 623-3000

Attorneys for Defendant

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. Defendant.	)	CIVIL ACTION No: 04-1418 (DMC)

ANSWER AND COUNTERCLAIMS OF TEVA PHARMACEUTICALS USA, INC.

Defendant Teva Pharmaceuticals USA, Inc. ("Teva") hereby responds to the First Amended Complaint of Pfizer Inc., Pharmacia & Upjohn Company, and Pfizer Health AB (collectively, "Pfizer") as follows:

THE PARTIES

1. Teva is without sufficient knowledge or information to form a belief as to the truth of the allegations of paragraph 1.

2. Teva is without sufficient knowledge or information to form a belief as to the truth of the allegations of paragraph 2.

3. Teva is without sufficient knowledge or information to form a belief as to the truth

of the allegations of paragraph 3.

4. Teva admits that it is a corporation organized and existing under the laws of the State of Delaware, and having a place of business at 1090 Horsham Road, North Wales Pennsylvania.

JURISDICTION AND VENUE

5. The allegation of paragraph 5 is a conclusion of law to which no response is required.

6. Teva admits the allegation of paragraph 6.

7. Teva admits that it sells generic drug products in the State of New Jersey and in various other locations in the United States.

8. The allegation of paragraph 8 is a conclusion of law to which no response is required. For the purposes of this litigation only, Teva does not contest personal jurisdiction in the United States District Court for the District of New Jersey.

9. The allegation of paragraph 9 is a conclusion of law to which no response is required. For the purposes of this litigation only, Teva does not contest personal jurisdiction in this district.

10. The allegation of paragraph 10 is a conclusion of law to which no response is required. For the purposes of this litigation only, Teva does not contest venue in this district.

The '600 Patent

11. Teva admits that United States Patent No. 5,382,600 (the "'600 Patent") is entitled "3,3-Diphenylpropylamines and Pharmaceutical Compositions Thereof" and that it was issued by the United States Patent and Trademark Office on January 17, 1995. Teva admits that

Pharmacia Aktiebolag is listed as the assignee on the face of the '600 Patent. Teva admits that what appears to be a true and correct copy of the '600 Patent is attached as Exhibit A to the First Amended Complaint. Teva is without sufficient knowledge or information to form a belief as to the truth of the remaining allegations of paragraph 11.

12. The allegations of paragraph 12 state a conclusion of law and therefore, no response is required. Further answering, Teva states that the '600 Patent speaks for itself.

Detrol®

13. Teva admits that the electronic version of the Food and Drug Administration ("FDA") publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" ("Orange Book") identifies Pharmacia & Upjohn (rather than Pfizer, as alleged) as the holder of an approved New Drug Application for tolterodine tartrate tablets, in 1 and 2 mg dosages. Teva further admits that the Orange Book identifies the proprietary name of tolterodine tartrate tablets, in 1 and 2 mg dosages, as Detrol®. Teva is without sufficient knowledge or information to form a belief as to the truth of the remaining allegations of paragraph 13.

14. Teva admits that the '600 Patent is listed in the Orange Book with respect to the Detrol® drug product.

Teva's ANDA

15. Teva admits that it submitted Abbreviated New Drug Application ("ANDA") No. 76-966 seeking FDA approval to engage in the commercial manufacture, use, or sale of tolterodine tartrate tablets, in 1 and 2 mg dosages ("Teva's Tolterodine Product").

16. Teva denies the allegations of paragraph 16 except that it admits that ANDA 76-966 refers to NDA 020771. Further answering, Teva states that the language of ANDA 76-966

speaks for itself.

17. Teva admits that it sent to Pfizer Inc. and others a "Patent Certification Notice" ("Notice Letter") on February 18, 2003, stating that Teva had submitted ANDA No. 76-898, seeking approval of Teva's Tolterodine Product.

18. Teva denies the allegations of paragraph 18 except that it admits that the Notice Letter states that ANDA No. 76-898 contains certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV Certifications") that the claims of the '600 Patent are invalid or will not be infringed by the commercial manufacture, use, or sale of Teva's Tolterodine Product.

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 5,382,600

19. Each of preceding paragraphs 1 through 18 is incorporated as if fully set forth herein.

20. Teva denies the allegations of paragraph 20.

21. Teva denies the allegations of paragraph 21.

22. Teva denies the allegations of paragraph 22.

AFFIRMATIVE DEFENSES

FIRST AFFIRMATIVE DEFENSE

Invalidity of the '600 Patent.

23. All of the claims of the '600 Patent are invalid under 35 U.S.C. § 101 *et seq.*

SECOND AFFIRMATIVE DEFENSE

Unenforceability of the '600 Patent for Inequitable Conduct Before the Patent and Trademark Office - Failure to Disclose Material Prior Art References.

24. The '600 Patent is unenforceable because, upon information and belief, individuals with substantive involvement in the prosecution of the '600 Patent intentionally breached their duty of candor under 37 C.F.R. § 1.56 by intentionally failing to disclose German patent No. 1216318 (the "Undisclosed German '318 Patent") to the examiner during the prosecution of the '600 Patent despite their knowledge of the reference and its high degree of materiality. The '600 Patent is therefore rendered unenforceable by inequitable conduct.

Prosecution of the '600 Patent and Related Applications

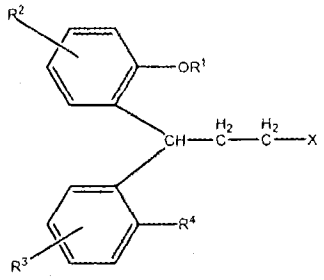
25. The '600 Patent issued from U.S. Patent Application Ser. No. 160,185 (the "'185 Application") entitled "3,3-Diphenylpropylamines and Pharmaceutical Compositions Thereof." The '185 Application was filed on December 19, 1991. At the time of filing, Kabi Vitrum AB, Stockholm, Sweden, was the designated assignee. The assignment was later changed to Pharmacia Aktiebiolag, Uppsala, Sweden, as appears on the face of the '600 Patent.

26. The '185 Application derived priority from an International Patent Cooperation Treaty ("PCT") Application No. 8900016 (the "'016 Priority Application"). The International Publication Number for the '016 Priority Application is WO8906644.

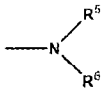
27. The '016 Priority Application was prosecuted by Kummelsten, Per Arne *et. al.*, attorneys from the Swedish law firm Uppsala Patentbyra. Bjorn Widen was an attorney at Uppsala Patentbyra, who was specifically named as a prosecuting attorney on national applications which resulted from the '016 Priority Application. Upon information and belief, Bjorn Widen participated in the prosecution of the '016 Priority Application.

28. The '185 Application and the issued '600 Patent both list Nils A. Jonsson, Bengt A. Sparf, Lembit Mikiver, Pinchas Moses, Lisbet Nilvebrant and Gunilla Glas as inventors.

29. The '185 Application described and claimed diphenylpropylamines of formula I:



wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II



wherein each of R^5 and R^6 independently signifies C_{1-6} alkyl, which may be joined to form a ring with the amine nitrogen and each of which may carry a hydroxy substituent, or adamantyl, and wherein R^5 and R^6 together contain at least three carbon atoms, preferably at least 4 carbon atoms, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

See Specification Submitted with the '185 Application, submitted 12/19/1991.

30. During prosecution of the '185 Application, the examiner rejected claims 1 to 4, 6 and 9 to 15 "under 35 U.S.C. § 103 as obvious over the German, British and U.S. patents and the Chemical Abstracts article cited in the corresponding PCT application [the '016 Priority Application]." The '016 Priority Application cited two British patents (GB 1169944 and GB 1169945), one U.S. patent (3,446,901), and Chemical Abstract, Vol. 97 (1982) 120105N. It did not cite any German patents. The examiner requested copies of "the German [and] British ... patents" from the Applicants for his review.

31. Despite the examiner's request for the German patent, Applicants, in their response, cited and produced to the examiner Danish Patent No. 111894 (the "Danish '894 Patent"). The Danish '894 Patent, on its face, claimed priority to a German Patent Application No. K48245, filed in November, 1962. This application issued as the Undisclosed German '318 Patent.

32. In response to the examiner's rejection, Applicants distinguished the Danish '894 Patent by arguing that it did not teach placing an OH or alkoxy substituent on the ortho position of the phenyl rings. The Undisclosed German '318 Patent, however, discloses an alkoxy substituent on the ortho position of the phenyl ring.

The Undisclosed German '318 Patent Was Cited to Applicants in a Related Foreign Patent Application

33. During the prosecution of the '185 Application, Swedish Application No. 92003318 (the "Swedish Metabolite Application") was filed on November 6, 1992. The specification and claims of the Swedish Metabolite Application were submitted as a PCT application, No. SE93/00927, on November 5, 1993 (the "PCT Metabolite Application").

34. The specification of the PCT Metabolite application specifically references the subject matter of the '185 Application and the compounds claimed in the PCT Metabolite Application only differ from those claimed in the '185 Application (as described in Formula I, paragraph 29 above) by one substituent group – the R^2 group in the PCT Metabolite Application is specified as a methanol group.

35. Three of the inventors identified in the '185 Application and the '600 Patent, Bengt A. Sparf, Pinchas Moses, and Lisbeth Nilvebrant, are also listed as inventors on the PCT Metabolite Application. In addition, the PCT Metabolite Application was prosecuted by Bjorn Widen, an attorney at Uppsala Patentbyra. Thus, inventors Bengt A. Sparf, Pinchas Moses, and Lisbeth Nilvebrant, and upon information and belief, attorney Bjorn Widen (hereinafter referred to collectively as "Applicants") participated in the prosecution of both the PCT Metabolite Application and the '185 Application (which issued as the '600 Patent).

A Reasonable Examiner Would Have Considered the Undisclosed German '318 Patent Highly Material to the Patentability of the '185 Application (which issued as the '600 Patent)

36. Regarding the PCT Metabolite Application, the examiner designated the Undisclosed German '318 Patent as type "X" in an International Search Report ("ISR") sent to Applicants on February 7, 1994. A type "X" reference is defined in the ISR as a "document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when taken alone."

37. Further regarding the PCT Metabolite Application, the examiner also designated WO8906644 (the formal publication of the '016 Priority Application, which is the predecessor of the '185 Application) as a type "X" reference. The examiner determined that the predecessor of the '185 Application was invalidating prior art and on that basis refused the PCT Metabolite

Application.

38. A reasonable examiner would have considered the Undisclosed German '318 Patent to be highly material to the patentability of the '185 Application for at least the following reasons: (1) the Undisclosed German '318 Patent was designated as particularly relevant prior art regarding the PCT Metabolite Application, which specifically references the subject matter of the '185 application and, with the exception of one substituent group, claims compounds identical to those claimed in the '185 Application, (2) the teachings of Undisclosed German '318 Patent are inconsistent with and would not have been distinguished by prior arguments made by Applicants, and (3) the Undisclosed German '318 Patent claims compounds that are also claimed in the '185 Application and the '600 Patent.

39. The Undisclosed German '318 Patent disclosed compounds that fall within the claims of the '600 Patent. Thus, the Undisclosed German '318 Patent anticipates the claims of the '600 Patent and/or renders the claims of the '600 Patent obvious. A reasonable examiner would therefore have considered the Undisclosed German '318 Patent highly material to the prosecution of the '185 Application.

The Applicants Failed to Disclose the Undisclosed German '318 Patent During the Prosecution of the '185 Application (which issued as the '600 Patent)

40. The Manual of Patent Examiner Procedure ("M.P.E.P.") in effect during prosecution of the '185 Application stated the following:

> Applicants and other individuals, as set forth in 37 C.F.R. 1.56, have a duty to bring to the attention of the Office any material prior art or other information cited or brought to their attention in any related foreign application. The inference that such prior art or other information is material is especially strong where it is the only prior art cited or where it has been used in rejecting the same or similar claims in the foreign application.

M.P.E.P. § 2001.06(a).

41. Therefore, Applicants had a duty to disclose information material to the patentability of the '185 Application to the United States Patent and Trademark Office.

42. Applicants had knowledge of the Undisclosed German '318 Patent while prosecuting the '185 Application. Applicants' knowledge is evidenced by the fact that the face of the Danish '894 Patent, which was provided to the examiner by Applicants, cites to the application for the Undisclosed German '318 Patent for priority, a fact which was highlighted by the examiner of the '185 Application's request for a German reference.

43. Applicants' knowledge of the Undisclosed German '318 Patent is further evidenced by their receipt of the February 7, 1994 ISR, which cited the Undisclosed German '318 Patent as invalidating prior art to the claims of the PCT Metabolite Application.

44. Applicants also had knowledge of the materiality of the Undisclosed German '318 Patent while prosecuting the '185 Application. Applicants' knowledge is evidenced by (1) the determination in the ISR that the Undisclosed German '318 Patent was of type "X", and therefore invalidated the claims of the Swedish Metabolite Application; (2) the fact that the Undisclosed German '318 Patent described a class of compounds which contained an alkoxy substituent, which description is inconsistent with and avoids Applicants' earlier argument for distinguishing the claimed compounds of the '185 Application from the related Danish '894 Patent; and (3) the fact that the Undisclosed German '318 Patent described a class of compounds identical to a subset of the claims of the '185 Application and the '600 Patent, and therefore anticipated those claims.

45. The Undisclosed German '318 Patent was never disclosed to the examiner during

prosecution of the '185 Application.

46. Upon information and belief, Applicants intentionally failed to cite the Undisclosed German '318 Patent to the examiner because it would have invalidated claims in the '185 Application (which issued as the '600 Patent).

47. As a result, upon information and belief, Applicants breached their duty of candor under 37 C.F.R. § 1.56 by intentionally failing to disclose the Undisclosed German '318 Patent to the examiner during the prosecution of the '185 Application despite their knowledge of the reference and its high degree of materiality. The '600 Patent is therefore rendered unenforceable by inequitable conduct.

TEVA'S COUNTERCLAIMS

For its Counterclaims, Teva alleges as follows:

THE PARTIES

48. Teva Pharmaceuticals USA, Inc. ("Teva") is a Delaware corporation with a principal place of business in North Wales, Pennsylvania.

49. Pfizer, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, NY.

50. Pharmacia & Upjohn Company is a corporation organized and existing under the laws of the State of Delaware having a place of business at 7000 Portage Road, Kalamazoo, MI. Pfizer, Inc. is ultimate parent of Pharmacia & Upjohn Company.

51. Pfizer Health AB is a company organized and existing under the laws of Sweden, having a place of business at Lindhagensgatan 100 SE-112 87, Stockholm, Sweden. Pfizer, Inc. is the ultimate parent of Pfizer Health AB. Pfizer Inc., Pharmaceia & Upjohn Company, and

Pfizer Health AB are hereinafter collectively referred to as "Pfizer."

JURISDICTION AND VENUE

52. These Counterclaims arise under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, and the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

53. This Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, 2202.

54. This Court has personal jurisdiction over Pfizer at least for the reason that Pfizer has submitted to the jurisdiction of this Court by virtue of filing its First Amended Complaint.

55. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE CONTROVERSY

56. In its First Amended Complaint, Pfizer asserts ownership of U.S. Patent No. 5,382,600 (the "'600 Patent") and alleges infringement of the '600 Patent by Teva.

57. Pursuant to the Federal Food, Drug, and Cosmetics Act, 21 U.S.C. §§ 355(j), Teva's ANDA No. 76-966 contains a certification by Teva stating that in its opinion, the '600 Patent is invalid, unenforceable or not infringed. Notice of that certification was sent to Pfizer.

58. Teva's importation, sale or offer for sale of Teva's proposed generic tolterodine tartrate tablets and the administration of those products within the United States will not infringe any valid or enforceable claim of the '600 Patent.

59. Upon information and belief, Pfizer's charge of infringement, after being advised by Teva as to why there is no basis for such charge, and other conduct yet to be discovered, renders this case exceptional within the meaning of 35 U.S.C. § 285.

COUNTERCLAIM 1

Declaratory Judgment of Invalidity of the '600 Patent

60. Teva realleges paragraphs 1-12 above as fully set forth herein.

61. An actual controversy exists between Teva and Pfizer concerning the validity of the '600 Patent, which requires a declaration of rights by this Court.

62. All claims of the '600 Patent are invalid for failing to comply with the requirements of the Patent Laws of the United States, 35 U.S.C. §§ 101, 102, 103 and 112.

COUNTERCLAIM 2

Declaratory Judgment of Unenforceability of the '600 Patent

63. Teva realleges paragraphs 1-15 above as fully set forth herein.

64. The '600 Patent is unenforceable because, upon information and belief, individuals with substantive involvement in the prosecution of the '600 Patent intentionally breached their duty of candor under 37 C.F.R. § 1.56 by intentionally failing to disclose German patent No. 1216318 (the "Undisclosed German '318 Patent") to the examiner during the prosecution of the '600 Patent despite their knowledge of the reference and its high degree of materiality. The '600 Patent is therefore rendered unenforceable by inequitable conduct.

Prosecution of the '600 Patent and Related Applications

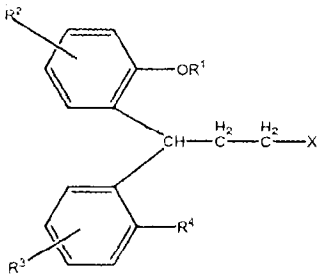
65. The '600 Patent issued from U.S. Patent Application Ser. No. 160,185 (the "'185 Application") entitled "3,3-Diphenylpropylamines and Pharmaceutical Compositions Thereof." The '185 Application was filed on December 19, 1991. At the time of filing, Kabi Vitrum AB, Stockholm, Sweden, was the designated assignee. The assignment was later changed to Pharmacia Aktiebiolag, Uppsala, Sweden, as appears on the face of the '600 Patent.

66. The '185 Application derived priority from an International Patent Cooperation Treaty ("PCT') Application No. 8900016 (the "'016 Priority Application"). The International Publication Number for the '016 Priority Application is WO8906644.

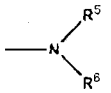
67. The '016 Priority Application was prosecuted by Kummelsten, Per Arne *et. al.*, attorneys from the Swedish law firm Uppsala Patentbyra. Bjorn Widen was an attorney at Uppsala Patentbyra, who was specifically named as a prosecuting attorney on national applications which resulted from the '016 Priority Application. Upon information and belief, Bjorn Widen participated in the prosecution of the '016 Priority Application.

68. The '185 Application and the issued '600 Patent both list Nils A. Jonsson, Bengt A. Sparf, Lembit Mikiver, Pinchas Moses, Lisbet Nilvebrant and Gunilla Glas as inventors.

69. The '185 Application described and claimed diphenylpropylamines of formula I:



wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphamoyl or halogen, and X represents a tertiary amino group of formula II



wherein each of R^5 and R^6 independently signifies C_{1-6} alkyl, which may be joined to form a ring with the amine nitrogen and each of which may carry a hydroxy substituent, or adamantyl, and wherein R^5 and R^6 together contain at least three carbon atoms, preferably at least 4 carbon atoms, their salts with physiologically acceptable acids and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

See Specification Submitted with the '185 Application, submitted 12/19/1991.

70. During prosecution of the '185 Application, the examiner rejected claims 1 to 4, 6 and 9 to 15 "under 35 U.S.C. § 103 as obvious over the German, British and U.S. patents and the Chemical Abstracts article cited in the corresponding PCT application [the '016 Priority Application]." The '016 Priority Application cited two British patents (GB 1169944 and GB 1169945), one U.S. patent (3,446,901), and Chemical Abstract, Vol. 97 (1982) 120105N. It did not cite any German patents. The examiner requested copies of "the German [and] British ... patents" from the Applicants for his review.

71. Despite the examiner's request for the German patent, Applicants, in their response, cited and produced to the examiner Danish Patent No. 111894 (the "Danish '894 Patent"). The Danish '894 Patent, on its face, claimed priority to a German Patent Application No. K48245, filed in November, 1962. This application issued as the Undisclosed German '318 Patent.

72. In response to the examiner's rejection, Applicants distinguished the Danish '894 Patent by arguing that it did not teach placing an OH or alkoxy substituent on the ortho position

of the phenyl rings. The Undisclosed German '318 Patent, however, discloses an alkoxy substituent on the ortho position of the phenyl ring.

The Undisclosed German '318 Patent Was Cited to Applicants in a Related Foreign Patent Application

73. During the prosecution of the '185 Application, Swedish Application No. 92003318 (the "Swedish Metabolite Application") was filed on November 6, 1992. The specification and claims of the Swedish Metabolite Application were submitted as a PCT application, No. SE93/00927, on November 5, 1993 (the "PCT Metabolite Application").

74. The specification of the PCT Metabolite application specifically references the subject matter of the '185 Application and the compounds claimed in the PCT Metabolite Application only differ from those claimed in the '185 Application (as described in Formula I, paragraph 22 above) by one substituent group – the R^2 group in the PCT Metabolite Application is specified as a methanol group.

75. Three of the inventors identified in the '185 Application and the '600 Patent, Bengt A. Sparf, Pinchas Moses, and Lisbeth Nilvebrant, are also listed as inventors on the PCT Metabolite Application. In addition, the PCT Metabolite Application was prosecuted by Bjorn Widen, an attorney at Uppsala Patentbyra. Thus, inventors Bengt A. Sparf, Pinchas Moses, and Lisbeth Nilvebrant, and upon information and belief, attorney Bjorn Widen (hereinafter referred to collectively as "Applicants") participated in the prosecution of both the PCT Metabolite Application and the '185 Application (which issued as the '600 Patent).

A Reasonable Examiner Would Have Considered the Undisclosed German '318 Patent Highly Material to the Patentability of the '185 Application (which issued as the '600 Patent)

76. Regarding the PCT Metabolite Application, the examiner designated the

Undisclosed German '318 Patent as type "X" in an International Search Report ("ISR") sent to Applicants on February 7, 1994. A type "X" reference is defined in the ISR as a "document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when taken alone."

77. Further regarding the PCT Metabolite Application, the examiner also designated WO8906644 (the formal publication of the '016 Priority Application, which is the predecessor of the '185 Application) as a type "X" reference. The examiner determined that the predecessor of the '185 Application was invalidating prior art and on that basis refused the PCT Metabolite Application.

78. A reasonable examiner would have considered the Undisclosed German '318 Patent to be highly material to the patentability of the '185 Application for at least the following reasons: (1) the Undisclosed German '318 Patent was designated as particularly relevant prior art regarding the PCT Metabolite Application, which specifically references the subject matter of the '185 application and, with the exception of one substituent group, claims compounds identical to those claimed in the '185 Application, (2) the teachings of Undisclosed German '318 Patent are inconsistent with and would not have been distinguished by prior arguments made by Applicants, and (3) the Undisclosed German '318 Patent claims compounds that are also claimed in the '185 Application and the '600 Patent.

79. The Undisclosed German '318 Patent disclosed compounds that fall within the claims of the '600 Patent. Thus, the Undisclosed German '318 Patent anticipates the claims of the '600 Patent and/or renders the claims of the '600 Patent obvious. A reasonable examiner would therefore have considered the Undisclosed German '318 Patent highly material to the

prosecution of the '185 Application.

The Applicants Failed to Disclose the Undisclosed German '318 Patent During the Prosecution of the '185 Application (which issued as the '600 Patent)

80. The Manual of Patent Examiner Procedure ("M.P.E.P.") in effect during prosecution of the '185 Application stated the following:

> Applicants and other individuals, as set forth in 37 C.F.R. 1.56, have a duty to bring to the attention of the Office any material prior art or other information cited or brought to their attention in any related foreign application. The inference that such prior art or other information is material is especially strong where it is the only prior art cited or where it has been used in rejecting the same or similar claims in the foreign application.

M.P.E.P. § 2001.06(a).

81. Therefore, Applicants had a duty to disclose information material to the patentability of the '185 Application to the United States Patent and Trademark Office.

82. Applicants had knowledge of the Undisclosed German '318 Patent while prosecuting the '185 Application. Applicants' knowledge is evidenced by the fact that the face of the Danish '894 Patent, which was provided to the examiner by Applicants, cites to the application for the Undisclosed German '318 Patent for priority, a fact which was highlighted by the examiner of the '185 Application's request for a German reference.

83. Applicants' knowledge of the Undisclosed German '318 Patent is further evidenced by their receipt of the February 7, 1994 ISR, which cited the Undisclosed German '318 Patent as invalidating prior art to the claims of the PCT Metabolite Application.

84. Applicants also had knowledge of the materiality of the Undisclosed German '318 Patent while prosecuting the '185 Application. Applicants' knowledge is evidenced by (1) the determination in the ISR that the Undisclosed German '318 Patent was of type "X", and therefore invalidated the claims of the Swedish Metabolite Application; (2) the fact that the

Undisclosed German '318 Patent described a class of compounds which contained an alkoxy substituent, which description is inconsistent with and avoids Applicants' earlier argument for distinguishing the claimed compounds of the '185 Application from the related Danish '894 Patent; and (3) the fact that the Undisclosed German '318 Patent described a class of compounds identical to a subset of the claims of the '185 Application and the '600 Patent, and therefore anticipated those claims.

85. The Undisclosed German '318 Patent was never disclosed to the examiner during prosecution of the '185 Application.

86. Upon information and belief, Applicants intentionally failed to cite the Undisclosed German '318 Patent to the examiner because it would have invalidated claims in the '185 Application (which issued as the '600 Patent).

87. As a result, upon information and belief, Applicants breached their duty of candor under 37 C.F.R. § 1.56 by intentionally failing to disclose the Undisclosed German '318 Patent to the examiner during the prosecution of the '185 Application despite their knowledge of the reference and its high degree of materiality.

88. An actual controversy exists between Teva and Pfizer concerning the enforceability of the '600 Patent, which requires a declaration of rights by this Court.

89. The '600 patent is unenforceable due to Pfizer's inequitable conduct during the prosecution of the '600 Patent.

PRAYER FOR RELIEF

Wherefore, Teva prays that this Court:

A. Enter judgment that Teva's Tolterodine Product does not infringe any valid or

enforceable claim of the U.S. Patent No. 5,382,600;

B. Enter declaratory judgment that U.S. Patent No. 5,382,600 is invalid;

C. Enter declaratory judgment that U.S. Patent No. 5,382,600 is unenforceable for inequitable conduct;

D. Enter an order dismissing Pfizer's Complaint, with prejudice, and denying the relief requested in the Complaint;

E. Declare the case exceptional and award Teva reasonable attorneys' fees and costs; and

F. Grant such other and further relief as the Court deems proper and just.

Dated: Newark, New Jersey
May 24, 2004

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	:	Docket No.: 04-1418 (DMC) Civil Action **STATEMENT OF TEVA PHARMACEUTICALS USA, INC. PURSUANT TO FEDERAL RULE OF CIVIL PROCEDURE 7.1(a)**

Pursuant to Rule 7.1(a) of the Federal Rules of Civil Procedure, defendant Teva Pharmaceuticals USA, Inc., hereby discloses that (1) its parent companies are: Orvet UK Ltd., Teva Pharmaceuticals Europe (Holland) and Teva Pharmaceutical Industries Ltd. (Israel); and (2) Teva Pharmaceutical Industries Ltd. is the only publicly-traded company that owns – through the aforementioned chain – 10% or more of Teva Pharmaceuticals USA, Inc.

Dated: May 24, 2004

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EXHIBIT 6

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB, Plaintiffs, v. IVAX PHARMACEUTICALS, INC., Defendant.	**C. A. No. 07-0174 (DMC) (MF)**
TEVA PHARMACEUTICALS USA, INC., Counterclaim-Plaintiff, v. PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB, Counterclaim-Defendants.	

PFIZER'S REPLY AND COUNTERCLAIM TO THE ANSWER AND COUNTERCLAIMS OF IVAX PHARMACEUTICALS, INC. AND TEVA PHARMACEUTICALS USA, INC.

Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company, and Pfizer Health AB (collectively, "Pfizer"), by their attorneys White & Case LLP and Gibbons P.C., for their Reply and Counterclaim to the Answer and Counterclaims of Defendant IVAX Pharmaceuticals, Inc. ("IVAX") and Counterclaim-Plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), herein allege:

Paragraphs 1 through 22 of IVAX and Teva's Answer and Counterclaims respond to paragraphs 1 through 22 of Pfizer's Complaint in this action. Paragraphs 23 through 77 of the Answer and Counterclaims set forth IVAX's affirmative defenses. Accordingly, paragraphs 1 through 77 of IVAX and Teva's Answer and Counterclaims are not replied to herein, except that, to the extent that response is required, Pfizer denies paragraphs 1 through 77 of the same.

REPLY TO COUNTERCLAIMS

Pfizer responds to the numbered allegations of IVAX and Teva's Counterclaims as follows. In responding to the Counterclaims, Pfizer does not waive its right to amend its Complaint to add Teva as a Defendant.

1. Pfizer admits the allegations of paragraph 1.

2. Pfizer admits the allegations of paragraph 2.

3. Pfizer is without knowledge or information sufficient to form a belief as to the allegations of paragraph 3.

4. Pfizer admits that Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York.

5. Pfizer admits that Pharmacia & Upjohn Company is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 7000 Portage

Road, Kalamazoo, Michigan. Pfizer also admits that Pfizer Inc. is the ultimate parent of Pharmacia & Upjohn Company.

6. Pfizer admits that Pfizer Health AB is a company organized and existing under the laws of Sweden, having a place of business at Lindhagensgatan 100 SE-112 87, Stockholm, Sweden. Pfizer also admits that Pfizer Inc. is the ultimate parent of Pfizer Health AB.

7. Pfizer neither admits nor denies the allegations of paragraph 7 because only conclusions of law are set forth therein.

8. Pfizer neither admits nor denies the allegations of paragraph 8 because only conclusions of law are set forth therein.

9. Pfizer admits that it filed the Complaint in this action. Pfizer neither admits nor denies the remaining allegations of paragraph 9 as they set forth only conclusions of law.

10. Pfizer neither admits nor denies the allegations of paragraph 10 because only conclusions of law are set forth therein.

11. Pfizer admits the allegations of paragraph 11.

12. Pfizer admits that, by letter dated January 10, 2007, IVAX purported to notify Pfizer of the submission to the United States Food and Drug Administration of an amendment to Abbreviated New Drug Application No. 77-006, and that, by such notification, IVAX alleged that it had made a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) concerning U.S. Patent No. 5,382,600 (the "'600 patent"). Pfizer is without knowledge or information sufficient to form a belief as to the remaining allegations of paragraph 12.

13. Pfizer denies that Teva's importation, sale or offer for sale of IVAX's *tolterodine* product and the administration of those products within the United States will not infringe any

valid or enforceable claim of the '600 patent. Pfizer is without knowledge or information sufficient to form a belief as to the remaining allegations of paragraph 13.

14. Pfizer denies the allegations of paragraph 14.

15. Pfizer admits that IVAX and Teva reallage paragraphs 1 through 14. Pfizer hereby realleges and incorporates by reference the averments of paragraphs 1 through 14 of this Reply.

16. Pfizer neither admits nor denies the allegations of paragraph 16 because only conclusions of law are set forth therein.

17. Pfizer denies the allegations of paragraph 17.

18. Pfizer admits that IVAX and Teva reallage paragraphs 1 through 17. Pfizer hereby realleges and incorporates by reference the averments of paragraphs 1 through 17 of this Reply.

19. Pfizer admits the allegations of paragraph 19.

20. Pfizer admits that, pursuant to 37 C.F.R. § 1.56, as interpreted by the U.S. Court of Appeals for the Federal Circuit and other courts, an "individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [United States Patent and Trademark] Office." Pfizer also admits that Nils A. Jönsson, Bengt A. Sparf, Lembit Mikiver, Pinchas Moses, Lisbet [sic] Nilvebrant, and Gunilla Glas are named as inventors of the '600 patent, and that Per Arne Kummelsten and Björn Widén were Swedish patent attorneys who were periodically involved in certain aspects of the prosecution of the application(s) leading to the '600 patent. Pfizer denies the remaining allegations of paragraph 20, including any legal conclusion in those allegations as to whether and during what time any individual had any duty to the United States Patent and Trademark Office under 37 C.F.R. § 1.56

or otherwise, with respect to the filing and prosecution of the application(s) leading to the '600 patent.

21. Pfizer admits that IVAX and Teva have quoted a passage that appears in section 2001.06(a) of certain editions of the M.P.E.P. Pfizer otherwise denies the allegations of paragraph 21.

22. Pfizer denies the allegations of paragraph 22.

23. Pfizer denies the allegations of paragraph 23.

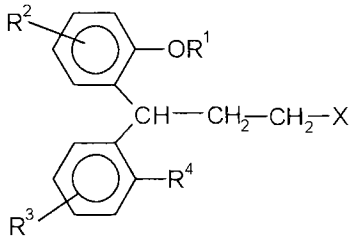
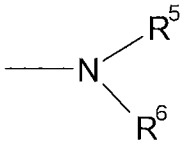
24. Pfizer admits that the '600 patent issued directly from the United States Application Serial No. 07/810,185 (the "U.S. Basic Application"), that the U.S. Basic Application was filed on December 19, 1991, that the U.S. Basic Application was assigned to Kabi Vitrum AB at the time of filing, and that Pharmacia Aktiebolag is the assignee listed on the face of the '600 patent. Pfizer otherwise denies the allegations of paragraph 24.

25. Pfizer admits that the U.S. Basic Application claimed priority to Swedish Patent Application No. 8800207-6 (the "Swedish Basic Application"), that the Swedish Basic Application was filed on January 22, 1988, that the Swedish Basic Application was converted into International Application No. PCT/SE89/00016 (the "Basic PCT") on January 20, 1989, and that the Basic PCT received International Publication No. WO 89/06644 (the "Basic Publication"). Pfizer otherwise denies the allegations of paragraph 25.

26. Pfizer admits that Per Arne Kummelsten and Björn Widén were, for some time on or after the filing date of the Swedish Basic Application, Swedish patent attorneys affiliated with Uppsala Patentbyra. Pfizer also admits that "KUMMELSTEN, Per, Arne et al.; Uppsala Patentbyra" are the listed agents on the Basic Publication. Pfizer denies the remaining allegations of paragraph 26.

27. Pfizer admits that both the U.S. Basic Application and the '600 patent list Nils A. Jönsson, Bengt A. Sparf, Lembit Mikiver, Pinchas Moses, Lisbet [sic] Nilvebrant, and Gunilla Glas as inventors.

28. Pfizer admits that the following is described beginning at line 4 of page 2 of the U.S. Basic Application:

> In the first aspect the invention provides novel 3,3-diphenylpropylamines of formula I
>
> 
>
> (I)
>
> wherein R^1 signifies hydrogen or methyl, R^2, R^3 and R^4 independently signify hydrogen, methyl, methoxy, hydroxy, carbamoyl, sulphanoyl or halogen, and X represents a tertiary amino group of formula II
>
> 
>
> (II)
>
> wherein R^5 and R^6 signify non-aromatic hydrocarbol groups, which may be the same or different and which together contain at least three carbon atoms, preferably at least four carbon atoms, especially at least five carbon atoms, and wherein R^5 and R^6 may form a ring together with the amine nitrogen, said ring preferably having no other hetero atom than the amine nitrogen.
>
> The compounds of formula I can form salts with physiologically acceptable acids, organic and inorganic, and the invention comprises the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide, hydrogen fumarate, and the like.

> When the novel compounds can be in the form of optical isomers, the invention comprises the racemic mixture as well as the individual enantiomers as such.
>
> A preferred sub-class of compounds according to the invention comprises tertiary amines of formula I, wherein each of R^5 and R^6 independently signifies C_{1-8}-alkyl, especially C_{1-6} alkyl, or adamantyl, R^5 and R^6 together comprising at least three, preferably at least four carbon atoms. R^5 and R^6 may carry one or more hydroxy groups, and they may be joined to form a ring together with the amine nitrogen atom.

Pfizer does not otherwise respond to the allegations of paragraph 28, as only conclusions of law are set forth therein.

29. Pfizer admits that, during the prosecution of the U.S. Basic Application, in an Office Action dated July 10, 1992, the examiner stated:

> Claims 1 to 4, 6 and 9 to 15 are rejected under 35 U.S.C. § 103 as being unpatentable over the German, British and US. patents and the Chemical Abstracts article cited in the corresponding PCT application. It is requested that copies of the German and British patents be supplied to complete the record.

Pfizer admits that the International Search Report generated in connection with the Basic PCT cited Great Britain Patent Nos. 1,169,944 and 1,169,945, U.S. Patent No. 3,446,901 (the "'901 patent"), and Chemical Abstracts Vol. 97 (1982) abstract 120105N, in addition to other references. Pfizer further admits that no German patents were cited in the International Search Report generated in connection with the Basic PCT. Pfizer otherwise denies the allegations of paragraph 29.

30. Pfizer admits that the applicants provided a copy of Danish Patent No. 111,894 (the "Danish '894 Patent"), cited in the International Search Report generated in connection with the Basic PCT, to the examiner during the prosecution of the U.S. Basic Application. Pfizer further admits that the Danish '894 Patent states that priority was requested from (West) German Patent Application No. K48,245 (the "German Application"), and that reference to the German

Application is made in (West) German Patent No. 1216318 (the "German '318 Patent"). Pfizer denies the remaining allegations of paragraph 30.

31. Pfizer denies the allegations of paragraph 31.

32. Pfizer admits that, during the pendency of the U.S. Basic Application, Swedish Patent Application No. 9203318-2 (the "Swedish Metabolite Application") was filed on November 6, 1992. Pfizer further admits that the Swedish Metabolite Application was converted into International Application No. PCT/SE93/00927 (the "Metabolite PCT") on November 5, 1993. Pfizer otherwise denies the allegations of paragraph 32.

33. Pfizer admits that the specification of the published Metabolite PCT references the Basic Publication. Pfizer denies the remaining allegations of paragraph 33.

34. Pfizer admits that Bengt A. Sparf, Pinchas Moses, and Lisbeth Nilvebrant are listed as inventors on the U.S. Basic Application, the '600 patent, and the Metabolite PCT. Pfizer also admits that "WIDEN, Björn et al.; Kabi Pharmacia AB" are the listed agents on the published Metabolite PCT. Pfizer denies the remaining allegations of paragraph 34.

35. Pfizer admits that an International Search Report, with a date of mailing of February 7, 1994, was generated in connection with the Metabolite PCT, and that it lists the German '318 Patent as a category "X" reference. Pfizer also admits that a category "X" reference is defined in that International Search Report as a "document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone." Pfizer denies the remaining allegations of paragraph 35.

36. Pfizer admits that the International Search Report generated in connection with Metabolite PCT lists the Basic Publication as a category "X" reference. Pfizer denies the remaining allegations of paragraph 36.

37. Pfizer denies the allegations of paragraph 37.

38. Pfizer denies the allegations of paragraph 38.

39. Pfizer admits that the applicants did not provide a copy of the German '318 Patent to the examiner during the prosecution of the U.S. Basic Application. Pfizer denies the remaining allegations of paragraph 39.

40. Pfizer admits that the applicants provided a copy of the Danish '894 Patent, cited in the International Search Report generated in connection with the Basic PCT, to the examiner during the prosecution of the U.S. Basic Application. Pfizer further admits that the Danish '894 Patent states that priority was requested from the German Application, and that reference to the German Application is made in the German '318 Patent. Pfizer denies the remaining allegations of paragraph 40.

41. Pfizer admits that, during the prosecution of the U.S. Basic Application, in an Amendment dated January 11, 1993, the applicants stated:

> In particular, [the Danish '894 Patent] is concerned with a process for preparing certain diphenylalkylamines that have particular effect on the heart and circulation. The particular compounds suggested therein are primary or secondary amines, but do not contain any OH or alkoxy substituent in the ortho position of the phenyl rings.

Pfizer denies the remaining allegations of paragraph 41.

42. Pfizer denies the allegations of paragraph 42.

43. Pfizer admits that both the Danish '894 Patent and Swedish Patent No. 300 822 (the "Swedish '822 Patent") state that priority was requested from the German Application, and

that reference to the German Application is made in the German '318 Patent. Pfizer denies the remaining allegations of paragraph 43.

44. Pfizer admits that, during the prosecution of the U.S. Basic Application, in an Amendment dated January 11, 1993, the applicants stated:

> In particular, [the Danish '894 Patent] is concerned with a process for preparing certain diphenylalkylamines that have particular effect on the heart and circulation. The particular compounds suggested therein are primary or secondary amines, but do not contain any OH or alkoxy substituent in the ortho position of the phenyl rings.

Pfizer denies the remaining allegations of paragraph 44.

45. Pfizer denies the allegations of paragraph 45.

46. Pfizer denies the allegations of paragraph 46.

47. Pfizer denies the allegations of paragraph 47.

48. Pfizer denies the allegations of paragraph 48.

49. Pfizer admits that, during the prosecution of the U.S. Basic Application, the examiner cited the '901 patent as a basis for rejecting certain then-pending claims. Pfizer admits that, during the prosecution of the U.S. Basic Application, in an Office Action dated July 10, 1992, the examiner stated:

> Claims 1 to 4, 6 and 9 to 15 are rejected under 35 U.S.C. § 103 as being unpatentable over the German, British and U.S. patents and the Chemical Abstracts article cited in the corresponding PCT application. It is requested that copies of the German and British patents be supplied to complete the record. These references disclose structurally related products. Selection from within a genus is held within the skill of the worker in the art absent a show of unexpected properties.

Pfizer also admits that, during the prosecution of the U.S. Basic Application, in an Office Action dated February 27, 1993, the examiner stated:

> Claims 1-4, 6, 9, 10, and 16 are rejected under 35 U.S.C. 103 as being obvious over Jones of record. The British patents of record have been dropped as being cumulative and the Danish patent and Vol. 97 Chemical

> Abstracts article have been overcome by applicants' arguments. Jones generically teaches the present compounds and specifically discloses the dimethylamino lower homolog. Applicants' showing in the specification has been considered but is not seen convincing because the closest compound of the present claims containing three carbon atoms (ethylmethylamino) has not been compared. Further, the significance of the data is not seen.

Pfizer denies the remaining allegations of paragraph 49.

50. Pfizer denies the allegations of paragraph 50.

51. Pfizer denies the allegations of paragraph 51.

52. Pfizer admits that, during the prosecution of the U.S. Basic Application, in a Response dated September 1, 1993, the applicants stated:

> [I]n general, the tests, including the table on page 43 ff, clearly shows [sic] that the claimed compounds have improved selectivity between the desired anticholinergic effect and undesired side effects.
>
> Since Jones is not concerned with anticholinergic agents, the selection of substituents to arrive at the compounds of the present invention would merely be fortuitous without any reasonable degree of expectation that the properties achieved by the present invention would be obtained. Furthermore, Jones is even more remote with respect to compounds reciting 'at least four carbon atoms.'

Pfizer denies the remaining allegations of paragraph 52.

53. Pfizer denies the allegations of paragraph 53.

54. Pfizer denies the allegations of paragraph 54.

55. Pfizer denies the allegations of paragraph 55.

56. Pfizer denies the allegations of paragraph 56.

57. Pfizer admits that, during the prosecution of the applications that led to the '600 patent, the applicants submitted "test results" for "compounds according to the invention," and "for comparison purposes," for N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, a compound disclosed in the '901 patent. Pfizer also admits that, during the prosecution of the

U.S. Basic Application, in a Response dated September 1, 1993, the applicants stated that "the specification includes a comparison of the claimed invention and the N,N-dimethyl-3-(2-methoxy phenyl)-3-phenylpropyl amine, which is considered to be the closest prior art compound that has been fabricated." Pfizer further admits that, during the prosecution of the U.S. Basic Application, in a Response dated April 22, 1994, the applicants amended one of the then-pending claims to require that "R^5 and R^6 together contain at least four carbon atoms." Pfizer denies the remaining allegations of paragraph 57.

58. Pfizer denies the allegations of paragraph 58.

59. Pfizer denies the allegations of paragraph 59.

60. Pfizer admits that, during the prosecution of the applications that led to the '600 patent, the applicants submitted "test results" for "compounds according to the invention," and "for comparison purposes," for N,N-dimethyl-3-(2-methoxyphenyl)-3-phenylpropylamine, a compound disclosed in the '901 patent. Pfizer also admits that, during the prosecution of the U.S. Basic Application, in a Response dated April 22, 1994, the applicants stated:

> [A]dditional comparative tests have been conducted in which the following two compounds according to the invention – in which R^5 plus R^6 contain four carbon atoms – have been compared with the dimethylamino compound according to Jones...
>
> The first compound (A) is a 2-methoxyphenyl compound and the second compound (B) is a 2-hydroxyphenyl compound. The compound (B) has an IC_{50} for anticholinergic effect of 180 nmoles and the compound (A) has an IC_{50} for anticholinergic effect of 220 nmoles. This means that compound [sic] (A) and (B) are approximately seven times better than the compound according to Jones (see the Table on page 43 in the present application).

Pfizer denies the remaining allegations of paragraph 60.

61. Pfizer denies the allegations of paragraph 61.

62. Pfizer denies the allegations of paragraph 62.

63. Pfizer denies the allegations of paragraph 63.

64. Pfizer denies the allegations of paragraph 64.

65. Pfizer admits that, during the prosecution of the U.S. Basic Application, the applicants submitted a declaration under 37 C.F.R. 1.132 of inventor Dr. Lisbeth Nilvebrant, dated June 23, 1994 (the "Nilvebrant Declaration"). Pfizer denies the remaining allegations of paragraph 65.

66. Pfizer admits that the Nilvebrant Declaration stated, in part:

> The comparative tests reported in Exhibit A attached to this declaration were conducted by me and/or under my direction and supervision.
>
> The results reported in Exhibit A are the values that were obtained from the comparative tests. These tests establish that the compounds (A) and (B) that were tested are approximately six to seven times better than the compound according to Jones, with respect to anticholinergic activity (see tables on page 43 of the above application).

Pfizer denies the remaining allegations of paragraph 66.

67. Pfizer denies the allegations of paragraph 67.

68. Pfizer denies the allegations of paragraph 68.

69. Pfizer denies the allegations of paragraph 69.

70. Pfizer denies the allegations of paragraph 70.

71. Pfizer denies the allegations of paragraph 71.

72. Pfizer denies the allegations of paragraph 72

* * *

Pfizer denies that IVAX and Teva are entitled to the relief sought in items (A-F) on pages 37 to 38 of their Counterclaims.

AFFIRMATIVE DEFENSES TO COUNTERCLAIMS

1. Counterclaim-Defendants Pfizer Inc., Pharmacia & Upjohn Company, and Pfizer Health AB (collectively, "Pfizer") hereby reallege and incorporate by reference the allegations set forth in the Complaint in this action.

2. U.S. Patent No. 5,382,600 (the "'600 patent") is valid.

3. The '600 patent is enforceable.

4. IVAX Pharmaceuticals, Inc. ("IVAX") and Teva Pharmaceuticals U.S.A., Inc.'s ("Teva") Counterclaims are barred, in whole or in part, because they fail to state a claim upon which relief may be granted.

5. The Court lacks subject matter jurisdiction over IVAX and Teva's Counterclaims, as pled.

COUNTERCLAIM AGAINST TEVA PHARMACEUTICALS USA, INC.

Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company, and Pfizer Health AB (collectively, "Pfizer"), by its attorneys White & Case LLP and Gibbons P.C., for their Counterclaim against "Counterclaim-Plaintiff" Teva Pharmaceuticals USA, Inc., herein allege:

THE PARTIES

1. Plaintiff Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York.

2. Plaintiff Pharmacia & Upjohn Company is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 7000 Portage Road, Kalamazoo, Michigan. Pfizer Inc. is the ultimate parent of Pharmacia & Upjohn Company.

3. Pfizer Health AB is a company organized and existing under the laws of Sweden, having a place of business at Lindhagensgatan 100 SE-112 87, Stockholm, Sweden. Pfizer Inc. is the ultimate parent of Pfizer Health AB.

4. Upon information and belief, IVAX Pharmaceuticals, Inc. ("IVAX") is a corporation organized and existing under the laws of the State of Florida, having its principal place of business at 4400 Biscayne Blvd., Miami, FL 33137.

5. Upon information and belief, Teva Pharmaceuticals USA, Inc. ("Teva") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business in North Wales, PA.

6. Upon information and belief, IVAX's parent company, IVAX Corp., was acquired by Teva's parent company, Teva Pharmaceutical Industries, Ltd., on or about January 26, 2006.

JURISDICTION AND VENUE

7. This Court has exclusive subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. Upon information and belief, Teva is in the business of making and selling generic drug products.

9. Upon information and belief, Teva sells and contracts to sell generic drug products in the United States, including the State of New Jersey.

10. Upon information and belief, Teva has submitted to the jurisdiction of the United States District Court for the District of New Jersey.

11. Teva is subject to personal jurisdiction in this judicial district.

12. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and

1400(b).

U.S. Patent No. 5,382,600

13. On January 17, 1995, the United States Patent and Trademark Office issued United States Patent No. 5,382,600 (the "'600 patent"), entitled "3,3-Diphenylpropylamines and Pharmaceutical Compositions Thereof." At that time of issue, the '600 patent was assigned to Pharmacia Aktiebolag. Pfizer Health AB currently holds title to the '600 patent. A copy of the '600 patent is attached to the Complaint in this action.

14. The '600 patent is directed to and claims, inter alia, 3,3 diphenylpropylamino derivatives and pharmaceutical compositions thereof, including tolterodine tartrate.

Detrol®

15. Pfizer holds an approved New Drug Application ("NDA") for tolterodine tartrate tablets, in 1 and 2 mg dosages, which it sells under the trade name Detrol® (the "Detrol NDA").

16. Pursuant to 21 U.S.C. § 355(b)(1) and attendant United States Food and Drug Administration ("FDA") regulations, the '600 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Detrol®.

IVAX's ANDA

17. Upon information and belief, IVAX submitted Abbreviated New Drug Application No. 77-006 to the FDA pursuant to 21 U.S.C. §§ 355(j) (the "IVAX ANDA"), seeking approval to market tolterodine tartrate tablets, in 1 and 2 mg dosages (the "IVAX Product").

18. Upon information and belief, the IVAX ANDA refers to and relies upon the Detrol NDA and purports to contain data showing bioequivalence of the IVAX Product with Detrol®.

19. On or about January 10, 2007, Pfizer received from IVAX a letter and attached memorandum, dated January 10, 2007 (collectively, the "IVAX Notification"), stating that IVAX had amended its ANDA to include a certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '600 patent is invalid, unenforceable, or not infringed by the manufacture, use, or sale of the IVAX Product (the "Paragraph IV Certification"). IVAX further stated that the amendment to its ANDA was submitted to obtain approval to engage in the commercial manufacture, use, or sale of the IVAX Product prior to the expiration of the '600 patent.

COUNT FOR INFRINGEMENT OF U.S. PATENT NO. 5,382,600 AGAINST TEVA

20. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-19 of this Counterclaim.

21. Upon information and belief, and as Teva and IVAX admit in paragraph 13 of IVAX and Teva's Counterclaims, substantially all of IVAX's business and operations, including all marketing, sales and distribution functions, have been integrated into Teva.

22. Upon information and belief, after Teva's parent company acquired IVAX's parent company, Teva made the business decision to pursue the IVAX Product, rather than its own generic formulation.

23. Upon information and belief, Teva was involved in the amendment of IVAX's ANDA to include a Paragraph IV Certification with respect to the '600 patent.

24. Upon information and belief, and as Teva and IVAX admit in paragraph

13 of IVAX and Teva's Counterclaims, Teva handles the marketing, sale and distribution of all IVAX products and Teva intends to import, sell or offer to sell the IVAX Product if and when that product receives FDA approval.

25. Teva has infringed the '600 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by participating in IVAX's amendment of ANDA No. 77-006, by which IVAX seeks approval from the FDA to engage in the commercial manufacture, use, or sale of the IVAX Product prior to the expiration of the '600 patent.

26. Teva has actively induced infringement of the '600 patent, pursuant to 35 U.S.C. § 271(b), by participating in IVAX's amendment of ANDA No. 77-006, by which IVAX seeks approval from the FDA to engage in the commercial manufacture, use, or sale of the IVAX Product prior to the expiration of the '600 patent.

27. Upon information and belief, Teva has knowingly and willfully infringed and induced infringement of the '600 patent.

28. Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '600 patent.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company, and Pfizer Health AB (collectively, "Pfizer") pray for a judgment in their favor and against IVAX Pharmaceuticals, Inc. ("IVAX") and Teva Pharmaceuticals USA, Inc. ("Teva"), as follows:

A. Entering judgment for Pfizer on their claims for infringement of U.S. Patent No. 5,382,600 (the "'600 patent") against IVAX and Teva;

B. Declaring that the '600 patent is valid and enforceable;

C. Dismissing IVAX and Teva's Counterclaims with prejudice;

D. Entering preliminary and permanent judgment enjoining IVAX and Teva from making, using, selling, offering to sell, or importing the product described in IVAX's ANDA No. 77-006 until after the expiration of the '600 patent;

E. Determining that this is an exceptional case under 35 U.S.C. § 285;

F. Awarding Pfizer its attorneys' fees, costs, and expenses incurred in defending against IVAX and Teva's Counterclaims; and

G. Awarding Pfizer such other and further relief as the Court deems just and equitable.

Dated: March 30, 2007
Newark, New Jersey

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EXHIBIT 7

Westlaw

Not Reported in F.Supp.2d
Not Reported in F.Supp.2d, 2005 WL 366966 (E.D.Tex.)
(Cite as: 2005 WL 366966 (E.D.Tex.))

Only the Westlaw citation is currently available.

United States District Court,
E.D. Texas, Marshall Division.
CONNECTEL, LLC Plaintiff
v.
CISCO SYSTEMS, INC. Defendant
No. 2:04-CV-396.

Feb. 16, 2005.

Mark A. Calhoun, Daniel Francisco Perez and Sanford E. Warren, Jr. of Winstead, Sechrest & Minick, Dallas, TX Earl Glenn Thames, Jr. of Potter Minton, Tyler, TX, for Plaintiffs.

Adam R. Alper and Eric R. Lamison of Kirkland & Ellis, LLP, San Francisco, CA Samuel Franklin Baxter of Marshall, TX John M. Desmarais of Kirkland & Ellis, New York, NY, for Defendants.

ORDER DENYING CISCO'S MOTION TO TRANSFER

DAVIS, J.

***1** Before the Court is Defendant Cisco Systems, Inc.'s ("Defendant" or "Cisco") Motion to Transfer to the Eastern District of Pennsylvania (Docket No. 11). For the reasons set forth below, the Court DENIES the motion.

BACKGROUND

Plaintiff ConnecTel, LLC ("Plaintiff" or "ConnecTel") accuses Cisco of infringing U.S. Patent Nos. 6,016,307 ("the '307 patent"), 6,144,641 ("the '641 patent"), 6,456,594 ("the '594 patent"), and 6,473,404 ("the ' 404 patent"). ConnecTel is allegedly the assignee of all four patents-in-suit, all of which deal with ConnecTel's intelligent routing technology. Because ConnecTel twice litigated the '307 patent in the Eastern District of Pennsylvania, Cisco contends that this case should be transferred to Judge James Knoll Gardner in the Eastern District of Pennsylvania, pursuant to 28 U.S.C. § 1404(a).

In May 2000, ConnecTel filed its first complaint in the Eastern District of Pennsylvania, accusing ITXC, Inc. of infringing the '307 patent. Judge Stuart Dalzell presided over most of the discovery and pre-trial motions until the case was assigned to Judge Gardner in December 2002. In February 2004, Judge Gardner held a *Markman* hearing to construe two claims relating to the terms "property of the data file" and "measuring said variable parameters" in the '307 patent. Judge Gardner issued his construction of those claims in March 2004, but shortly thereafter, ConnecTel settled its suit with ITXC.

In June 2000, ConnecTel filed its second complaint in the Eastern District of Pennsylvania, accusing Arbinet Holdings of infringing the '307 patent. In response to ConnecTel's complaint, Arbinet (a New York-based company) moved to dismiss for lack of personal jurisdiction, or in the alternative, to transfer the case from the Eastern District of Pennsylvania to the Southern District of New York. The case was transferred to the Southern District of New York and subsequently dismissed by agreement of the parties.

In November 2004, ConnecTel filed this action against Cisco. Cisco asserts that this action, like the two previous actions, could have been filed in the Eastern District of Pennsylvania, but does not contest the jurisdiction of this Court to hear the matter.

ANALYSIS

Section 1404(a) allows a district court "[f]or the convenience of parties and witnesses, in the interest of justice" to transfer a case to any other district or division where the case might have been brought. 28 U.S.C. § 1404(a) (2003). Section 1404(a) protects litigants, witnesses, and the public against unnecessary inconvenience and expense, and avoids wasted time, energy, and money. *Van Dusen v. Barrack*, 376 U.S. 612, 616 (1964). It is within the district court's discretion to decide whether to transfer venue, and the moving party bears the burden of showing why the court should transfer the case to a

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different forum. *Hanby v. Shell Oil Co.*, 144 F.Supp.2d 673, 676 (E.D.Tex.2001).

The first determination to be made under 28 U.S.C. § 1404(a) is whether the claim could have been filed in the judicial district to which transfer is sought. *In re Volkswagen AG*, 371 F.3d 201, 203 (5th Cir.2004). If so, under section 1404(a), a court examines "the convenience of the parties and witnesses." *Id.* When examining convenience, the district court balances the private interests of the litigants and the public interests of fair and efficient administration of justice. *International Software Sys., Inc. v. Amplicon, Inc.*, 77 F.3d 112, 115 (5th Cir.1996). To transfer a case, a district court must find that the balance of the private and public interests substantially favor transfer. *See, e.g., Peteet v. Dow Chem. Co.*, 868 F.2d 1428, 1436 (5th Cir.1989); *Howell v. Tanner*, 650 F.2d 610, 616 (5th Cir.1981); *Menendez Rodriguez v. Pan Am. Life Ins. Co.*, 311 F.2d 429, 434 (5th Cir.1962)("whether it be by transfer order under the statute or by dismissal under the doctrine of forum non conveniens, the plaintiff's privilege to choose, or not to be ousted from, his chosen forum is highly esteemed"); *LeDoux v. Isle of Capri Casinos Inc.*, 218 F.Supp.2d 835, 837 (E.D.Tex.2002); *Mohamed v. Mazda Motor Corp.*, 90 F.Supp.2d 757, 771-74 (E.D.Tex.2000); *see also Gulf Oil Corp. v. Gilbert*, 330 U.S. 501, 508 (1947).

***2** The following factors can be considered in weighing private interest: (a) plaintiff's choice of forum, (b) convenience and location of witnesses and the parties, (c) cost of obtaining the attendance of witnesses and other trial costs, (d) place of the alleged wrong, (e) accessibility and location of sources of proof, and (f) possibility of delay and prejudice if transfer is granted. *See Gulf Oil*, 330 U.S. at 508. The following factors can be considered in weighing the public interest: (a) administrative difficulty, (b) localized interests in resolving localized controversies, (c) jurors' time, and (d) conflict of laws. *See Mohamed*, 90 F.Supp.2d at 771. Though all of these factors are considered to the extent they are applicable, none are given dispositive weight. *See In re Volkswagen AG*, 371 F.3d at 203.

Because the parties do not dispute--and the Court agrees--that this action could have been brought in the Eastern District of Pennsylvania, the Court now turns to the convenience determination. The private and public factors each will be discussed in turn below.

A. Private Interest Factors

The first factor involves the plaintiff's choice of forum. Though the plaintiff's choice of forum is "in and of itself ... neither conclusive nor determinative," *In re Horshoe Entm't.*, 337 F.3d 429, 434 (5th Cir.2003), the plaintiff's choice of forum is nonetheless entitled to some deference. *See, e.g., Mohamed*, 90 F.Supp.2d at 771-74. Cisco contends that ConnecTel's choice of forum should not be entitled to deference since the Eastern District of Texas "bears little or no relation" to the underlying the cause of action. *Cognitronics Imaging Sys., Inc. v. Recognition Research Inc.*, 83 F.Supp.2d. 689, 696 (E.D.Va.2000). However, Cisco sells the accused infringing products in the Eastern District of Texas, and "sale of allegedly infringing products in the Eastern District of Texas ... is an event that is significant and relevant," to an underlying cause of action. *Cummins-Allison Corp., v. Glory Ltd.*, 2004 WL 1635534 at *5 (E.D.Tex.2004)(Ward, J.). Furthermore, Cisco has significant operations in Richardson, a community located within the Eastern District of Texas. The Court thus concludes that ConnecTel's choice of the Eastern District of Texas as forum for this litigation is entitled to some deference, so this factor does not favor transfer.

The second factor considers the location of the parties and witnesses. Cisco notes that ConnecTel has an office in Horsham, Pennsylvania--a community located in the Eastern District of Pennsylvania--and that one of the named inventors on the patents resides in Erie, Pennsylvania. [FN1] However, convenience to a plaintiff "is not a consideration" when analyzing a defendant's motion to transfer since the plaintiff chose the forum and presumably considered convenience and cost. *Cum-*

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mins-Allison, 2004 WL 1635534 at *5 (citing 15 Charles Alan Wright & Arthur R. Miller, *Federal Practice and Procedure* § 3849 (West 1986)). Cisco has not established that litigating in the Eastern District of Texas is significantly less convenient than litigating in the Eastern District of Pennsylvania. Indeed, litigating here could actually be more convenient for Cisco and its witnesses, since although Cisco is headquartered in San Jose, California, it has six offices across the state of Texas, including a technical center in Richardson, Texas. Thus, the second factor does not favor transfer.

> FN1. Erie is in the Western District of Pennsylvania. The other named inventor, presumably someone who will also be called as a witness, resides in Miami, Florida.

***3** Similarly, the third factor does not favor transfer, as Cisco has not established that the parties would enjoy cost savings from litigating in the Eastern District of Pennsylvania instead of the Eastern District of Texas.

The fourth factor involves the place of the alleged wrong. In a patent case involving the nationwide sale of allegedly infringing goods, a patent-owner may bring its action in any forum where the alleged infringement occurred. *See Beam Laser Sys., Inc. v. Cox Communications, Inc.*, 117 F.Supp.2d 515, 518- 519 (E.D.Va.2000). Because the allegedly infringing goods were sold in the Eastern District of Texas, the fourth factor does not favor transfer.

The fifth factor involves the accessibility and location of sources of proof. Given that patent cases like this involve battles of documents and technical experts scattered across the nation, this factor is immaterial and thus does not favor transfer.

The sixth factor considers the possibility of delay or prejudice if transfer is granted or denied. Cisco contends that because Judge Gardner has familiarity with the technology and with the '307 patent, the case would be resolved faster and perhaps more accurately if transferred. However, Judge Gardner would be required to construe many other claims in the '307 patent and achieve familiarity with three other patents. Thus, Judge Gardner's familiarity with the '307 patent would not necessarily lead to a more rapid resolution of the case, so this factor is, at best, neutral.

B. Public Interest Factors

The first public factor is similar to the sixth private factor discussed above and considers the administrative difficulties in granting or denying transfer. Cisco contends that because the '307 patent has an extensive litigation history in the Eastern District of Pennsylvania, transfer is favored to capitalize on the transferee court's familiarity with the facts, legal issues, and parties. However, Cisco's contention is rather tenuous, since Judge Gardner merely construed two terms found in one of the four patents at issue. The present case involves a different defendant and different products, so it is not in the interest of judicial economy to transfer this case.

Cisco further contends that transfer is appropriate because the transferee court previously construed some claims in the '307 patent. The Court has previously recognized the serious problem of inconsistent constructions of the same claims by different courts. *See Logan v. Hormel Foods Corp., et al.*, case no. 6:04-cv-211; *MyMail, Ltd. v. America Online, Inc.*, 223 F.R.D. 455 (E.D.Tex.2004). However, in both cases, the Court analyzed the problem of inconsistent claim constructions--and subsequent motions to transfer--in the context of the case as a whole. Thus, the Court granted the motion to transfer in *Logan,* but denied the motion to transfer in *MyMail.*

In *Logan,* the plaintiff alleged infringement of certain claims in the '374 patent. Previously, the plaintiff had alleged infringement of many, if not all, of these claims in the Southern District of Texas. *See Logan v. HoneyBaked L.P.*, No. H-01-1611 (S.D.Tex. Apr. 5, 2004)(Werlein, J.). After Judge Ewing Werlein, Jr. issued an exhaustive claim construction opinion, the Southern District case settled. Upon motion by the defendant in the

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Eastern District case, the Court transferred the case to Judge Werlein because Judge Werlein had previously construed many of the claims at issue. The Court concluded that transfer was in the interest of judicial economy because Judge Werlein would be able to draw on his familiarity with the patent--particularly its eleven years of prosecution history--when issuing, if necessary, a new claim construction and seeing the case to final resolution. The Court also concluded that the plaintiff was bringing suit in the Eastern District in an attempt to obtain a more favorable claim construction ruling. Forum shopping for a different claim construction is undesirable because of the uncertainty those different constructions may generate over the scope of patent rights. Thus, viewed in the context of the entire case, this Court concluded that transfer was clearly warranted.

***4** *Logan* however is distinguishable from this case since, as discussed above, the gains in judicial economy are at best minimal, and possibly non-existent since such gains could be realized by simply referring to Jude Gardner's claim construction, if necessary. Though the '307 patent has litigation history in the Eastern District of Pennsylvania, this case involves more than just construing claims that were previously construed by Judge Gardner. Four patents, with potentially hundreds of claims to construe, are at issue here. Given the number of claims at issue, Judge Gardner's previous claim construction does not determine the fate of this case. And again, although not bound by Judge Gardner's claim construction opinion, *RF Del., Inc. v. Pac. Keystone Techs., Inc.*, 326 F.3d 1255, 1261 (Fed.Cir.2003), the Court can refer to Judge Gardner's claim construction if it is concerned about an inconsistent ruling. Thus, the Court concludes that when viewing this case on the whole, the same concerns that motivated transfer in *Logan* are simply not present here.

Likewise, the inconsistent claim construction problems present in *MyMail* are not present here. *MyMail* involved a motion to sever and then transfer part of the patent suit. The Court denied both motions because it did not want to create two ongoing cases involving the same patent in different districts. Two ongoing cases would require a duplication of judicial resources during discovery, particularly the claim construction phase, and could ultimately lead to different adjudications of the same patent. For all of these reasons, the Court concludes that the first public interest factor is at best neutral towards transfer.

The second and third public interest factors involve the localized interest in resolving localized controversies and the burdening of citizens in the forum with jury duty. "The residents of the Eastern District of Texas ... have a significant interest in the enforcement of federal patent laws against infringement activities occurring within the division." *Cummins-Allison*, 2004 WL 1635534 at *5. If this case goes to trial, the residents of the Eastern District of Texas will not be burdened by jury duty any more than the residents of the Eastern District of Pennsylvania would be burdened. Therefore, these factors do not weigh in favor of transfer.

The fourth factor involves any conflict of laws. Since this action is brought under a federal statute, and since that statute's interpretation is governed by the law of the Federal Circuit in both this forum and in the Eastern District of Pennsylvania, this factor does not weigh in favor of transfer.

CONCLUSION

Because Cisco has failed to demonstrate why ConnecTel's choice of the Eastern District of Texas as the forum for this litigation should be disturbed, the motion is DENIED.

So ORDERED.

Not Reported in F.Supp.2d, 2005 WL 366966 (E.D.Tex.)

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EXHIBIT 8

Only the Westlaw citation is currently available.

United States District Court,
E.D. Texas, Marshall Division.
DATAMIZE, INC. Plaintiff,
v.
FIDELITY BROKERAGE SERVICES, LLC, et al., Defendants.
No. 2:03-CV-321-DF.

April 22, 2004.
of last filing July 16, 2004.
filed Sept. 5, 2003.

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Laura R Braden, Fish & Richardson PC--Boston, Boston, MA, Attorney to be Noticed, representing Fidelity Brokerage Service LLC, (Defendant).

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Nicholas B Clifford, Jr, Tompson Coburn, St Louis, MO, Attorney to be Noticed, representing Scottrade Inc, (Counter Claimant).

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Danny Lloyd Williams, Williams Morgan & Amerson PC, Houston, TX, Lead Attorney, Attorney to be Noticed, representing TradeStation Securities Inc, (Counter Claimant).

ORDER

FOLSOM, J.

***1** Before the Court are Joining Defendants' Motion to Transfer (Dkt. No. 25), Datamize's Response and Sur-Reply (Dkt. Nos. 51 & 67), and Defendants' Reply (Dkt. No. 60). After having reviewed the applicable law and facts of this case, and after having conducted a hearing on this matter on March 11, 2004, for the following reasons Defendants' Motion is DENIED.

I. BACKGROUND

This is a patent infringement case brought by Datamize, Inc., against nine Defendants. Datamize is a small, start-up company, incorporated in Wyoming with its principal place of business in Missoula, Montana. Datamize developed a software product named MyPortal™, protected by U.S. Patent Nos. 6,014,137 (the '137 patent) and 6,460,040 (the '040 patent). MyPortal allows computer users to select financial data information from both local and networked internet sources and allows users to format a portion of the information displayed on a computer screen.

Defendants are online brokerage companies that provide its customers with online trading platforms. Defendants have their principal places of business in Boston, Massachusetts, St. Louis, Missouri, Greenwich, Connecticut, New York, New York, San Francisco, California, Austin, Texas, Plantation, Florida, and Chicago, Illinois, and are incorporated in Delaware, Arizona, Connecticut, California, Texas, Florida, and Illinois. Defendants' trading platforms allow their customers to select commercial financial information relevant to a customer's individual interests and format the display of the information on a computer screen. Defendants derive their revenue from fees charged their customers based on the number of trades customers place.

On May 17, 2002, Datamize filed suit against Plumtree Software, Inc., a non-party to the present case, for infringement of the '137 patent in the United States District Court of Montana. Plumtree is a Delaware corporation with its principal place of business in San Francisco, California. Plumtree sells software "enterprise portal" products to corporations for private use by corporate employees. Plumtree's portal products do not enable public commercial financial transactions. Plumtree derives revenue from its enterprise portals based on the number of employees that use its software for in house purposes versus commercial financial transactions.

In the Montana action, Plumtree filed a motion to dismiss for lack of personal jurisdiction or, alternatively, to transfer the case to the Northern District of California. The case was referred to Magistrate Judge Leif Erickson, who on November 23, 2002, issued a Report and Recommendation to grant Plumtree's motion to dismiss.

On December 4, 2002, subsequent to the magis-

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trate's recommendation and before the Montana district judge ruled on Plumtree's motion to dismiss, Plumtree filed an action in the Northern District of California, requesting a declaratory judgment that it does not infringe any valid and enforceable claim of the '137 patent. On July 8, 2003, the Montana district court officially adopted Magistrate Judge Erickson's findings and dismissed Datamize's action for infringement for lack of personal jurisdiction. Subsequently, on July 17, 2003, Datamize filed its answer in the Northern District of California action and counterclaimed for infringement of the '137 patent.

***2** Datamize filed a motion for realignment of the parties on August 7, 2003. On October 6, 2003, District Judge Vaughn Walker granted Datamize's motion finding the court had the power to realign the parties and that it was necessary to do so. *Plumtree Software, Inc ., v. Datamize, LLC,* No. C 02-5693 VRW, at 12 (N.D.Cal. Oct. 6, 2003) [hereafter Realignment Order].

On September 5, 2003, Datamize filed the present action against Defendants for infringement of the '040 patent. The '040 patent is a "child" of the "parent" '137 patent, *i.e.,* the application for the '040 patent was filed in the United States Patent and Trademark Office as a continuation application before the '137 patent issued. Both patents have the same priority date of February 27, 1996, which is the original filing date of the '137 patent. The '137 patent was issued on January 11, 2000, and the '040 patent was issued on October 1, 2002.

To avoid an obviousness-type double patenting rejection issued by the Patent Office, the inventor agreed to a terminal disclaimer that provided the '040 patent with the same expiration date as the '137 patent. Both patents are enforceable for 20 years from the date of filing of the '137 patent or until February 27, 2016.

In addition to their priority and expiration dates, the '137 and '040 patents share the same inventor, specification, drawings, and prosecuting attorney. The patents, however, have different claims, claim limitations, claim scopes, and prior art citations for consideration by the Court during any claim construction, infringement, or validity determinations. The claimed inventions also involve different technologies and accused products that will involve different damages theories and calculations the Court must consider.

In response to the action filed by Plaintiffs in this Court, Defendants filed their present Motion to Transfer to the Northern District of California. The issues to be considered by this Court include whether there is "substantial overlap" between the present case and the Northern District of California action, how the "first-filed" California action affects transfer to that District, and the private and public venue factors of 28 U.S.C. § 1404(a).

II. GENERAL RULES OF LAW

The Fifth Circuit generally follows the first-to-file rule. *See West Gulf Maritime Ass'n v. ILA Deep Sea Local,* 751 F.2d 721, 730 (5th Cir.1985). "The federal courts have long recognized that the principle of comity requires federal district courts--courts of coordinate jurisdiction and equal rank--to exercise care to avoid interference with each other's affairs." *Id.* at 728. The general principle in the interrelation of federal district courts is to avoid duplicative litigation. *Colorado River Water Conservation District v. United States,* 424 U.S. 800, 817 (1976). Federal courts should try to avoid the waste of this duplication as well as rulings that may trench upon the authority of sister courts and piecemeal resolution of issues that call for a uniform result. *West Gulf Maritime Ass'n,* 751 F.2d at 729.

***3** In deciding whether to apply the first-to-file rule, the Court must resolve two questions: (1) are the two pending actions so duplicative or do they involve such substantially similar issues that one court should decide the subject matter of both actions, and if so, (2) which of the two courts should take the case. *Texas Instruments v. Micron Semiconductor,* 815 F.Supp. 994, 997 (E.D.Tex.1993). "Once the likelihood of substantial overlap between the two suits has been demonstrated, it is no longer up to the second-filed court to resolve the question

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of whether both should be allowed to proceed." *Cadle Co. v. Whataburger of Alice, Inc.*, 174 F.3d 599, 605-06 (5th Cir.1999) (*citing Mann Mfg., Inc., v. Hortex, Inc.*, 439 F.2d 403, 407 (5th Cir.1971)). Instead, "the proper course of action [is] for the [second-filed] court to transfer the case" to the first-filed court. *Id.* at 606. It is then the responsibility of the first-filed court to decide "whether the second suit filed must be dismissed, stayed, or transferred and consolidated." *Sutter Corp. v. P & P Indus., Inc.*, 125 F.3d 914, 920 (5th Cir.1997).

28 U.S.C. § 1404(a) provides: "For the convenience of parties and witnesses, in the interest of justice, a district court may transfer any civil action to any other district or division where it might have been brought." The purpose of section 1404 is to prevent the waste of time, energy and money and to protect litigants, witnesses, and the public against unnecessary inconvenience and expense. *In re Triton Sec. Lit.*, 70 F.Supp.2d 678, 688 (E.D.Tex.1999).

Venue is primarily an issue of convenience. *Time, Inc. v. Manning*, 366 F.2d 690, 696 (5th Cir.1966). The decision to transfer rests within the discretion of the court. *Peteet v. Dow Chemical Co.*, 868 F.2d 1428, 1436 (5th Cir.1989). The decision to transfer venue is an "individualized, case-by-case consideration of convenience and fairness." *Stewart Org., Inc. v. Ricoh Corp.*, 487 U.S. 22, 29 (1988) (citation omitted). In determining whether to grant a motion to transfer under section 1404(a), a district court must balance the private convenience interests of the litigants and the public interests in the fair and efficient administration of justice. *In re Triton*, 70 F.Supp.2d at 688; *Robertson v. Kiamichi RR Co.*, 42 F.Supp.2d 651, 655 (E.D.Tex.1999).

III. DISCUSSION

A. SUBSTANTIAL SIMILARITY AND FIRST-TO-FILE RULE

The primary issue in this case is whether the California action and the current action are "duplicative" or involve "substantially similar" issues so as to require application of the first-to-file rule. In meeting this first requirement, it is enough that the "overall content of each suit is not very capable of independent development, and will be likely 'to overlap to a substantial degree.' " *Superior Sav. Ass'n v. Bank of Dallas*, 705 F.Supp. 326, 329 (N.D.Tex.1989) (quoting *Mann Mfg.*, 439 F.2d at 407, 408 n. 6)). The cases need not be identical to be duplicative. *Id.* at 329.

***4** The overlap in this case is not "substantial," otherwise requiring this Court to transfer the case to the Northern District of California because this case involves different defendants, different patent claims, different claim scopes, different accused products, and a different industry. The sole Defendant in the California action is Plumtree, who is not a co-Defendant in the present case. Defendants argue under Fifth Circuit law there is no requirement there be common defendants for substantial overlap to exist, citing *Save Power Ltd. v. Syntek Finance Corp.*, 121 F.3d 947, 951 (5th Cir.1997). Datamize, however, does not solely rely on the fact that different defendants exist in this case as did Save Power to argue insubstantial overlap.

In addition to different defendants, this case involves a different patent with different patent claims and claim scopes. When comparing the independent claims of the '137 and '040 patents, some notable differences exist. For instance, the independent claims of the '040 patent are more broad than those of the '137 patent. The independent claims of the '137 patent are more limited in scope as they include some important limitations not found in the '040 patent.

For example, Claim 1 of the '137 patent claims "a method for defining custom interface screens customized for individual kiosks...." Claims 1, 14, and 30 of the '040 patent more generally claim a method for presenting customized assortments of information. Accordingly, Claim 1 of the '137 patent is directed more specifically to defining custom interface screens, while Claims 1, 14, and 30 of the '040 patent are more generally directed to presenting information.

Claim 1 of the '137 patent additionally requires a

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"master database of information," "at least one pre-defined window type," "pre-defined button type," "pre-defined multimedia type," and "button type," and "assigning of values" to "attributes" not included in Claims 1, 14, or 30 of the '040 patent. These additional terms further differentiate the claim scopes of the ' 137 and '040 patents and provide further evidence of insubstantial overlap between the two patents.

Defendants argue Datamize cannot deny the two patents claim the same invention because the inventor filed a terminal disclaimer in response to a Patent Office obviousness-type double patenting rejection of the '040 patent claims over the claims in the issued '137 patent. The United States Court of Appeals for the Federal Circuit, having jurisdiction of all patent appeals under 28 U.S.C. § 1295, has made clear that patent applicants do not admit to obviousness-type double patenting by filing a terminal disclaimer that gives up a portion of their patent term beyond the expiration date of the parent patent. *Ortho Pharmaceutical Corp. v. Smith*, 959 F.2d 936, 941 (Fed.Cir.1992).

In other words, the Federal Circuit has rejected, in no uncertain terms, the argument that the claims of a continuation patent are obvious in light of its parent. The court in *Ortho* stated:

> *5 In essence, Ortho seems to be contending that, by filing a terminal disclaimer in the '322 patent, the applicants admit not only that the '322 claims are an obvious variation of the '911 claims but, also, that they are an obvious variation of any claims in a third patent from which the '911 claims are themselves invalid for double patenting. However, the critical premise to this argument (i.e., by filing the terminal disclaimer, the '322 applicants admitted to obviousness-type double patenting) is wrong. The terminal disclaimer filed in '322 did no more than give up the portion of the patent term beyond the expiration date of the '911 patent. It did not concede double patenting with relation to any other patent.

Id.

Accordingly, the fact the inventor of the '040 patent filed a terminal disclaimer is not evidence the claims of the '040 patent are obvious in light of the claims of the '137 patent, nor is it evidence of substantial overlap of the claim scope of the patents. "It is a fundamental principle of patent law that two applications cannot claim the same invention, so it is not possible that the ['040] patent discloses any of the methods covered by the claims of the ['137] patent. While the ['040] and ['137] patents may be within the same field of technology, the claims which must be examined to determine their validity do not cover the same invention." *Somafor Danek Holdings, Inc. v. U.S. Surgical Corp.*, 1998 U.S. Dist. LEXIS 21746, at *9-*10 (W.D.Tenn.1998).

No substantial overlap additionally exists because different products in different industries are accused of infringing the claims of the '040 patent versus those of the '137 patent. In the California action, Plumtree's corporate portal products are alleged to infringe the claims of the '137 patent.

A corporate portal is software designed to aggregate and display information of large corporate entities on private corporate networks, such as a corporate intranet that can be accessed by the corporation's employees. The corporate enterprise portal software is used for in house purposes and not for commercial financial transactions. Plumtree therefore derives its revenue from the number software licenses granted to companies based on the number of employees that use the enterprise software.

Defendants in the present action are online brokerage companies that provide its customers with online trading platforms. Defendants' trading platforms allow their customers to select commercial financial information relevant to a customer's individual interests and format the display of the information on a computer screen. Defendants derive their revenue from fees charged their customers based on the number of commercial trades customers place.

Defendants argue the nature of the accused products is irrelevant. Any differences in industries and product types are meaningless because the first

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step in any infringement analysis is interpretation of the claims at issue. Moreover, the Federal Circuit holds that "claim scope is determined without regard for the accused device." *Young Dental Mfg. Co., Inc. v. Q3 Prods., Inc.*, 112 F.3d 1137, 1141 (Fed.Cir.1997) (*citing General Mills, Inc. v. Hunt-Wesson, Inc.*, 103 F.3d 978, 981 (Fed.Cir.1997)).

***6** Claim construction is but one aspect of a patent infringement case. Defendants ignore the fact that different products involve different technology and functionality, which are two of the most dominant and time consuming components of a patent case in discovery or at trial. Different products also involve different damages theories and calculations and are but a couple examples of other time intensive components of patent cases that have little relation to claim construction.

Because different products from different industries are alleged to infringe the '137 and '040 patents, different issues are presented as to technology, infringement, and damages. These differences are further evidence of insubstantial overlap with the California action. *See Square D Co. v. Medar, Inc.*, 1994 U.S. Dist. LEXIS 20897, *8 (D.Del.1994) (denying motion to transfer due to no substantial overlap of technology or cases involving different products); *Agere Sys., Inc. v. Broadcom Corp.*, 2003 U.S. Dist. LEXIS 12636 (E. D.Pa.2003) (denying motion to transfer when patents and products were different).

Defendants argue the Court should transfer this case because based on the identical specifications of the '137 and '040 patents, similar claim construction issues and infringement and invalidity contentions will exist between the actions in California and this Court. Defendants also argue a danger exists that the two Courts may issue inconsistent claim construction rulings and cite this Court's ruling in *Medtronic Ave, Inc. v. Cordis Corp.*, No. 2:02-CV-73 (E .D. Tex. Mar. 19, 2003) for support.

The present case, however, involves different patents with different claims and claim scopes allegedly infringed by different products in different industries. The Federal Circuit has held that where there are even small differences in the language of claims in related patents, the claim language in each patent should be construed independently. *ResQnet.com, Inc. v. LANSA, Inc.*, 346 F.3d 1374, 1384 (Fed.Cir.2003) (finding the differences in claim language "significant" requiring the court to interpret "the claim anew, without regard to the interpretation" of the claims of the parent patent).

Defendants further argue this case should be transferred to the Northern District of California in light of the Federal Circuit's recent ruling in *Microsoft Corp. v. Multi-Tech Sys., Inc.*, Nos. 03-1138, 03-1139, 2004 WL 191013 (Fed.Cir. Feb. 3, 2004). The Court in *Microsoft* held that prosecution history estoppel applies to the claims of a parent patent based on statements made during prosecution of a child patent. *Id.* at *8. Accordingly, Defendants argue the prosecution history of the '040 patent will be relevant for claim construction of the claims of the '137 patent in the Northern District of California. This argument fails because the claims of the '137 patent are not at issue in the present action. Moreover, the claims of the ' 040 patent have different claim scopes that will require different claim interpretations and application of different prior art for claim construction, invalidity, and infringement purposes.

***7** Accordingly, few, if any, conflicting or overlapping rulings will occur between the two actions. Moreover, "the decision of the California court in the previous action is readily available to this court [or vice versa] for consultation" if this Court or the Northern District of California determine a particular claim term should be construed consistently. *See Somafor*, 1998 U.S. Dist. LEXIS 21746, at *11-*12 (denying for similar reasons motion to transfer to Central District of California and rejecting argument that grandparent/grandchild relationship between patents would create duplicative litigation).

B. APPLICATION OF FIRST-TO-FILE RULE

With regard to application of the first-to-file rule,

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this Court is not inflexible in its application of the rule. *Texas Instruments*, 815 F.Supp. at 997. Even though the first-to-file rule normally serves to promote efficiency and should therefore not be disregarded lightly, circumstances and modern judicial reality may periodically demand a different approach. *Id.* at 997 (citing *Church of Scientology of Cal. v. United States Dept. of the Army*, 611 F.2d 738, 750 (9th Cir.1979)). To avoid the application of the first-to-file rule, the party avoiding its application must show the existence of "compelling circumstances." *See Mann Mfg.*, 439 F.2d at 407; *Igloo Prods. Corp. v. Mounties, Inc.*, 735 F.Supp. 214, 217 (S.D. Tex 1990).

One such exception to the first-to-file rule is when the first-filed suit is filed in anticipation of the subsequent suit. *Amerada Petroleum Corp. v. Marshall*, 381 F.2d 661, 663 (5th Cir.1967). The facts indicate that Plumtree, the party to whom Defendants wish to join in the Northern District of California action, engaged in forum shopping by filing their declaratory judgment action while the Montana action was still pending.

Judge Walker in the Northern District of California expressly found that Plumtree had engaged in a blatant form of forum shopping. In his order to realign the parties, Judge Walker stated the case "does not present the usual rationale for bringing a declaratory judgment action." Realignment Order at 8- 9 (internal citations omitted). The Declaratory Judgment Act's function is to "relieve potential defendants from the Damoclean threat of impending litigation which a harassing adversary might brandish, while initiating suit at his leisure--or never." *Id.* (citation omitted). "Plumtree has gone to considerable lengths to deprive Datamize of its choice of forum ... and to have [the Montana] issues tried in the Northern District of California. Accordingly, it seems equitable to allow Datamize to retain its status as plaintiff, despite the loss of its choice of forum." *Id.* at 11.

Transferring this case to the Northern District of California, therefore, would compound the prejudice already caused to Datamize by depriving Datamize of its choice of forum in an insubstantially similar case that involves different defendants, patent claims, claim scopes, accused products, and industry. *See Villegas-Alanis v. Wurth,* 2001 U.S. Dist. LEXIS 23504, at *29, * 35-40 (W.D.Tex.2001) (finding first and second-filed cases only "partially duplicative of each other" and declining to apply first-filed rule when first-filed suit was initiated in anticipation of second-filed suit).

***8** In addition to *Mann Mfg.,* Defendants argue various cases from this District support the proposition that second-filed actions involving child patents should be transferred to first-filed actions involving parent patents. Moreover, because parent and child patents are in the same "family" of patents, overlap of subject matter between such patents is necessarily substantial warranting transfer. In support of this argument, Defendants cite *Mann Mfg.*, 439 F.2d at 408, *Charles Hill & Assocs., Inc. v. Amazon.com, Inc.,* No. 2:02- CV-186-TJW (E.D.Tex. Jan. 23, 2003), *Nat'l Instrument Corp. v. Software Tech., LLC,* No. 2:03-CV-47-TJW (E.D.Tex. May 9, 2003), and *Cal. Sec. Co-op, Inc. v. Multimedia Cablevision, Inc.*, 897 F.Supp. 316 (E.D.Tex.1995). Each of these cases involve similar parties and some of the same, if not same, patents and subject matter. These cases do not involve completely different defendants or different patent claims, claim scopes, accused products, and industry as does the present action.

Accordingly, based on the foregoing the Court finds the California action and the current action are not "duplicative" or involve "substantially similar" issues so as to require application of the first-to-file rule.

C. PRIVATE CONVENIENCE FACTORS OF 28 U.S.C. § 1404(a)

The party seeking transfer bears the burden of showing the convenience factors favor transfer. *Manning*, 366 F.2d at 698; *In re Triton*, 70 F.Supp.2d at 688. Moreover, the defendant seeking transfer cannot carry this burden by making unsup-

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ported assertions, but must properly establish the relevant facts. *In re Triton*, 70 F.Supp.2d at 688. The private convenience factors include: "(1) the plaintiff's choice of forum; (2) the relative ease of access to the sources of proof; (3) the cost of obtaining attendance of witnesses and other trial expenses; (4) the place of the alleged wrong; and, (5) the possibility of delay and prejudice if transfer is granted." *Id.*

1. Plaintiff's Choice of Forum

A plaintiff's right to choose a forum is "well-established," and his choice is usually highly esteemed. *Texas Instruments*, 815 F.Supp. at 996. The plaintiff's choice of a forum is "a paramount consideration in any determination of transfer request, and that choice should not be lightly disturbed." *Young v. Armstrong World Indus.*, 601 F.Supp. 399, 401 (N.D.Tex.1984) (citing *Shutte v. Armco Steel Corp.*, 431 F.2d 22, 25 (3d Cir.1970)).

Further, the judicial system inherently provides a plaintiff with his choice of forum:

> The existence of [forum choices] not only permits but indeed invites counsel in an adversary system, seeking to serve in his client's interests, to select the forum that he considers most receptive to his cause. The motive of the suitor in making this choice is ordinarily of no moment: a court may be selected because its docket moves rapidly, its discovery procedures are liberal, its jurors are generous, the rules of law applied are more favorable, or the judge who presides in that forum is thought more likely to rule in the litigant's favor.

***9** *McCuin v. Texas Power & Light Co.*, 714 F.2d 1255, 1261-62 (5th Cir.1983).

Defendants argue that because the Eastern District of Texas is not Datamize's home forum, "the usual deference accorded the plaintiff's choice is of minimal value," citing *Hanby v. Shell Oil Co.*, 144 F.Supp.2d 673, 677 (E.D.Tex.2001). In *Hanby* there was found to be no nexus of activity in the Eastern District of Texas where the plaintiffs had not claimed any infringing activity in the District. Datamize has made clear accusations against Defendants in the present action for patent infringement in this District. The Court thus finds the plaintiff's choice of forum factor weighs in favor of denying transfer to the Northern District of California.

2. Relative Ease of Access to the Sources of Proof

Defendants' argument that California is the more convenient forum because Datamize is currently litigating in California against Plumtree does not overcome Defendants' burden. The Court has found there is no substantial overlap between the present action and the action in the Northern District of California. Defendants are alleged to infringe the claims of the '040 patent in this District. Moreover, "the accessibility and location of sources of proof should weigh only slightly in this Court's transfer analysis, particularly since these factors have been given decreasing emphasis due to advances in copying technology and information storage." *Mohamed v. Mazda Motor Corp.*, 90 F.Supp.2d 757, 778 (E.D.Tex.2000); *Brock v. Baskin-Robbins USA Co.*, 113 F.Supp.2d 1078, 1089 (E.D.Tex.2000) ("As this Court has stated previously, when documents can be easily copied and shipped to the Eastern District, the Court does not consider their present location 'an important factor in the transfer analysis." ') (*citing In re Triton*, 70 F.Supp.2d at 690).

Defendants also argue they are not aware of any Datamize witnesses located in Texas; nor are Defendants aware of any defense witnesses located in the Eastern District of Texas. Because Defendants are unaware of any Datamize or defense witnesses located in Texas does not mean none exist. A generalized argument such as this does not overcome Defendants' burden.

Defendants argue the prosecuting attorney for both the '137 and '040 patents, who is one of only three witnesses listed in Datamize's Initial Disclosure Statement, resides in Northern California. The other two witnesses listed in Datamize's Initial Disclosure Statement are Datamize's cofounders who reside in

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Montana. Given Datamize has chosen this District to pursue the present action against Defendants and weight the Court affords plaintiffs with their choice of forum, the Court finds Datamize's witnesses would not be inconvenienced by having to travel to this Court.

Defendants further argue that considerable sources of prior art, such as prior art in the field of user interfaces and object-oriented programming, are certain to exist in the Northern District of California. This arguments dismisses the fact that the creation of user interfaces and object-oriented programming occurs throughout the United States and indeed the world. Moreover, any relevant prior art, whether from Silicon Valley or elsewhere, may easily be submitted to the Court given the convenience of modern-day mail and electronic services.

***10** Defendant also argues that named Defendant Charles Schwab & Co., Inc., is headquartered in Northern California and several of the other Defendants, including E*TRADE, Instinet, Scottrade, Terra Nova Trading, and Fidelity Brokerages maintain significant offices in Northern California. Eight of the nine Defendants, however, are neither incorporated in, nor have their principal place of business anywhere in California. These eight Defendants have their principal places of business in Boston, Massachusetts, St. Louis, Missouri, Greenwich, Connecticut, New York, New York, Austin, Texas, Plantation, Florida, and Chicago, Illinois, and are incorporated in Delaware, Arizona, Connecticut, Texas, Florida, and Illinois. Each of these locations are closer to the Eastern District of Texas than the Northern District of California.

The Court thus finds the relative ease of access to the sources of proof is satisfied by maintaining jurisdiction in the Eastern District of Texas.

3. The Cost of Obtaining Attendance of Witnesses and Other Trial Expenses

Defendants do not address the cost of obtaining the attendance of witnesses or the availability of compulsory process. Defendants therefore have not met their burden for this factor.

4. The Place of the Alleged Wrong

Defendants likewise do not address this factor. Furthermore, the alleged infringement at issue in this case takes place anywhere the Defendants' customers arguably infringe the claims of the '040 patent, including the Eastern District of Texas as asserted by Datamize.

5. The Possibility of Delay and Prejudice if Transfer is Granted

Datamize argues it may lose its set trial date of March 29, 2005, in the Northern District of California action if the present case is transferred to that Court. Defendants, however, argue that no delay will occur if the Court were to transfer this case to the Northern District of California. Because the California action was filed before the present action, the California case has progressed to a stage further than the present action. The present action could easily be consolidated with the case in California due to the similarity of subject matter, patents, and patent claims.

The Court finds that both actions are virtually at the same stage of litigation. The Montana District Court dismissed the Montana action on July 8, 2003, the action in this Court was filed on September 5, 2003, and the Realignment Order was issued by the Northern District of California on October 6, 2003. In addition, both actions are currently scheduled for trial in March 2005. Delay is therefore not a factor that weighs in favor of transfer and Defendants have failed to meet their burden.

Defendants further argue that prejudice will occur if a transfer is not granted due to the possibility of inconsistent rulings from two federal courts on the same issues. This inconsistency may include different claim construction rulings on the same claim terms. Moreover, transfer of this case would eliminate the progression of duplicative efforts on the part of this Court and the California Court and maximize the substantial resources already invested in the California action. Under the comprehensive Northern District of California Patent Local Rules designed to streamline complex patent litigation, sub-

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stantial efficiencies will be realized by consolidation with the California action.

***11** The Court finds no prejudice will occur if the Court denies transfer. The Court has found no substantial overlap exists between the two actions as there are different defendants, patent claims, claim scopes, accused products, and industries at issue. These differences will prevent inconsistent rulings or duplicative efforts between the two Courts. Moreover, this Court is not unfamiliar with patent infringement cases. Although the Court does not use local "patent rules" as explicitly adopted by the Northern District of California, at least similar efficiencies will be realized by maintaining the present action in the current District.

Accordingly, based on the foregoing analysis the Court finds the private interest factors weigh against transfer of the current action to the Northern District of California.

B. PUBLIC INTEREST FACTORS OF 28 U.S.C. § 1404(a)

The public interest factors include: "(1) the relative backlog and other administrative difficulties in the two jurisdictions; (2) the fairness of placing the burdens of jury duty on the citizens of the state with the greater interest in the dispute; (3) the local interest in adjudicating local disputes; and, (4) the appropriateness of having the case in a jurisdiction whose law will govern the dispute in order to avoid difficult problems in conflicts of laws." *In re Triton*, 70 F.Supp.2d at 688.

1. Administrative Difficulties

The current action and the action in the Northern District of California are at similar stages of litigation. Different issues exist between the two actions as to defendants, patent claims, claim scopes, accused products, and industries. These differences will prevent inconsistent rulings or duplicative efforts between the two Courts. Because different products from different industries are alleged to infringe the '137 and '040 patents, different issues will be presented as to technology, infringement, and damages. In addition, the Court is unaware of whether the Northern District of California has acquired any special expertise with regard to the technologies or issues in dispute.

Accordingly, no administrative difficulties exist to justify the transfer of this case to the Northern District of California.

2. Burdens of Jury Duty, and

3. Local Interest in Adjudicating Local Disputes

Defendants are large financial brokerage companies that enable stock trading on a nationwide basis over the internet. Defendants collectively have a strong national presence, including in the Eastern District of Texas where Defendants' products are accused of infringing the claims of '040 patent. As such, citizens of the Eastern District of Texas have an interest in adjudicating this dispute. *See In re Triton*, 70 F.Supp.2d at 691 ("The Court finds that the citizens of the Eastern District have a substantial interest in correcting any wrongdoing on the part of companies who trade stocks on a national basis.").

Moreover, Defendants have produced no evidence to support an argument there exists any greater burden on a potential jury in the Eastern District of Texas, a lesser burden on any jury in the Northern District of California, or a greater interest in the Northern District of California to try this case.

***12** Accordingly, the Court finds the greater interest in adjudicating this dispute lies in the Eastern District of Texas.

4. Conflicts of Laws

The parties do not contend and the Court does not find any choice of law conflicts that would arise if this case is not transferred.

Accordingly, based on the foregoing analysis the Court finds the public interest factors weigh against transfer of this case to the Northern District of California.

III. STAY OF PROCEEDINGS

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Defendants seek a limited stay pending further order of the transferee court (or this Court if the motion to transfer is denied) so that the court handling this matter can determine the most efficient manner to proceed. The Court denied Defendants' motion for stay at the March 11, 2004, hearing on Defendants' present Motion to Transfer. The parties should continue forward with all discovery under Local Rule CV-26(a) and until the parties' case management schedule is approved by the Court.

IV. CONCLUSION

Based on the foregoing analysis, the Court finds that transferring this case to the Northern District of California would not serve the interests of justice because there is insufficient overlap between the actions pending in this District and the Northern District of California. Although the actions involve parent and child patents having identical specifications, drawings, and inventors, the claims of the '040 patent are substantially different from the '137 patent as they are more broad than the claims of the '137 patent and have different terms and claim scopes. As a result of these differences, different defendants, different accused products, different technologies, different prior art, different claim constructions, and different industries are involved in the present action versus the action in the Northern District of California.

Datamize has chosen this forum to litigate its claims against the Defendants and the private and public interest factors of 28 U.S.C. § 1404(a) weigh against transfer of this case to the Northern District of California.

The Court therefore

ORDERS that Defendants' Motion to Transfer to the Northern District of California and motion for stay is DENIED.

Defendants' Motion for a Stay of Proceedings was DENIED at the March 11, 2004, hearing and is therefore MOOT.

Not Reported in F.Supp.2d, 2004 WL 1683171 (E.D.Tex.)

END OF DOCUMENT

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EXHIBIT 9

Only the Westlaw citation is currently available.

United States District Court, E.D. Pennsylvania.
SMITHKLINE BEECHAM CORPORATION and Beecham Group, P.L.C., Plaintiffs
v.
GENEVA PHARMACEUTICALS, INC., Defendant
No. Civ.A. 99-CV-2926.

Feb. 11, 2000.

Arthur Makadon, Ballard, Spahr, Andrews and Ingersoll, Phila, PA, Robert D. Bajefsky, Richard B. Racine, Finnegan, Henderson, Farabow, Garrett & Dunner, Washington, DC, Walter Y. Boyd, Jr., Ford F. Farabow, Jr., Finnegan, Henderson, Farabow, Garrett & Dunner, Atlanta, GA, Kenneth M. Frankel, Finnegan, Henderson, Farabow, Garrett & Dunner, Washington, DC, Sally A. Steffen, Ballard, Spahr, Andrews & Ingersoll, LLP, Phila, PA, for Smithkline Beecham Corporation, Plaintiff.

Arthur Makadon, Robert D. Bajefsky, Richard B. Racine, Walter Y. Boyd, Jr., Ford F. Farabow, Jr., Kenneth M. Frankel, Sally A. Steffen, (See above), for Beecham Group, P.L.C., Plaintiff.

Steven J. Lee, Kenyon & Kenyon, New York, NY, John B. Starr, Jr., Lynne Darcy, Kenyon & Kenyon, New York, NY, Alan K. Cotler, Klett, Lieber, Rooney & Schorling, P.C., Two Logan Square, Philadelphia, PA, for Geneva Pharmaceuticals, Inc., Defendant.

MEMORANDUM AND ORDER

KAUFFMAN, J.

*1 SmithKline Beecham Corporation ("SmithKline") a corporation with its headquarters and principal place of business in the Commonwealth of Pennsylvania, (Cplt. at ¶ 3) and Beecham Group, P.L.C. ("Beecham"), a corporation organized and existing under the laws of England with its principal place of business in Brentford, Middlesex, England (Cplt. at ¶ 5), commenced this action on June 9, 1999, charging Geneva Pharmaceuticals, Inc. ("Geneva") with patent infringement. [FN1] SmithKline alleges that Geneva's filing of an abbreviated new drug application for FDA approval of its marketing of paroxetine hydrochloride tablets would technically infringe SmithKline's U.S. Patent Nos. 4,721,723 ("the '723 patent"), 5,900,423 ("the '423 patent"), and 5,872,132 ("the '132 patent"). [FN2] Geneva is based in Broomfield, Colorado. (Def. Mot. at 3.) Now before the Court is Geneva's Motion to Transfer pursuant to 28 U.S.C. § 1404(a). For the reasons set forth below, the Motion will be denied.

FN1. The patent at issue in this case was assigned by Beecham to SmithKline on November 1, 1995. The assignment was recorded in the Patent and Trademark Office on January 22, 1996. (Cplt. at ¶ 5.)

FN2. Under the so-called Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act, codified as amended at 21 U.S.C. §§ 301 *et seq.*, a pharmaceutical manufacturer seeking expedited FDA approval to market a generic version of a patented drug may submit an abbreviated new drug application ("ANDA"). 21 U.S.C. § 355(j). To avoid patent infringement problems, the applicant must provide the Food and Drug Administration with a certificate establishing that the marketing of the generic drug will not infringe the patent for the listed drug. To this end, the applicant must certify that: (I) the patent information has not been filed, (II) the patent has expired, (III) the patent will expire on a specified date, or (IV) the "patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." 21 U.S.C. § 355(j)(2)(A)(vii). As part of a certification under Paragraph IV, the ANDA applicant must notify the patent holder and approved applicants of its application and include a

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> statement of the factual and legal basis for the applicant's opinion that the patent is not valid or will not be infringed. See 21 U.S.C. § 355(j)(2)(B).

Geneva moves the Court to transfer this Action to the Northern District of Illinois, where SmithKline has commenced an action against Apotex Corporation ("Apotex") charging Apotex with infringement of the '723 patent. *SmithKline Beecham Corp. v. Apotex Corp.,* No. 98 C 3952 (N.D. Ill. filed June 26, 1998) ("the Illinois Action"). In the Illinois Action, SmithKline argues that Apotex's application for the approval of "Paroxetine HC1 Tablets" infringes on SmithKline's patent entitled "Anti-Depressant Crystalline Paroxetine Hydrochloride Hemihydrate," which the United States Patent and Trademark Office granted on or about January 26, 1998. [FN3] Geneva contends that, "absent transfer of this case to the Northern District of Illinois, possibly overlapping issues relating to the construction of the claims of at least the '723 patent will be pending in both this District and the Northern District of Illinois." (Def. Mem. at 5.)

> FN3. The '723 patent claims crystalline paroxetine hydrochloride hemihydrate and its use in treating depression. *SmithKline Beecham Corp. v. Apotex Corp.*, No. 98 C 3952 1999 WL 311697, at *1 (N.D.Ill. May 13, 1999).

Title 28 U.S.C. § 1404(a) provides: "For the convenience of parties and witnesses, in the interest of justice, a district court may transfer any civil action to any other district or division where it might have been brought." 28 U.S.C. § 1404(a). The question before the Court, therefore, is whether Geneva has shown that "on balance the litigation would more conveniently proceed and the interests of justice be better served by transfer" to Illinois. 15 Charles Alan Wright *et al., Federal Practice and Procedure*, § 3847 (2d ed.1987) *quoted in Jumara v. State Farm Ins. Co.*, 55 F.3d 873, 879 (1995).

Although § 1404(a) refers only to "the convenience of parties and witnesses" and "the interests of justice," the court must consider all relevant factors to determine whether a transfer is warranted. *Jumara,* 55 F.3d at 879; 15 Charles Alan Wright *et al., Federal Practice and Procedure,* § 3847 (2d ed.1987). In this regard, the court examines both the private interests of the litigants and factors of public interest. *Gulf Oil Corp. v. Gilbert,* 330 U.S. 501, 508 (1947). Relevant private interests include the relative ease of access to sources of proof, the cost of obtaining attendance of witnesses, and "all other practical problems that make trial of a case easy, expeditious and inexpensive ." *Gulf Oil,* 330 U.S. at 508. Relevant factors of public interest include the avoidance of the potential for inconsistent judgments and the promotion of judicial economy. *See Gulf Oil,* 330 U.S. at 508. Section 1404(a) thus vests the district court with broad discretion "to adjudicate motions for transfer according to an 'individualized, case-by-case consideration of convenience and fairness.' " *Stewart Org., Inc. v. Ricoh Corp.*, 487 U.S. 22, 29 (1988) (quoting *Van Dusen v. Barrack*, 376 U.S. 612, 622 (1964)).

***2** Though the decision whether to transfer is left to the sound discretion of the court, the burden of demonstrating the desirability of transfer lies with the moving party. *Jumara,* 55 F.3d at 879. In addition, "a plaintiff's choice of a proper forum is a paramount consideration in any determination of a transfer request," and " 'should not be lightly disturbed." ' *Shutte v. Armco Steel Corp.*, 431 F.2d 22, 25 (3d Cir.1970) (quoting *Ungrund v. Cunningham Bros., Inc.*, 300 F.Supp. 270, 272 (S.D.Ill.1969)). Accordingly, unless the " 'balance of convenience of the parties is strongly in favor of the defendant, the plaintiff's choice of forum should prevail." ' *Shutte*, 431 F.2d at 25 (quoting *Owatonna Mfg. Co. v. Melroe Co.*, 301 F.Supp. 1296, 1307 (D.Minn.1969)).

Geneva argues that this action is duplicative of the Illinois Action and that a transfer would be more convenient for its witnesses, would promote judicial economy, and would avoid the potential for inconsistent judgments. (Def. Mem. at 8-9.) SmithKline responds, "In fact, the issue in the Chicago litigation is whether Apotex's product infringes the

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'723 patent; the issues in the Geneva litigation are whether Geneva's product infringes one, two, or all three of SmithKline's paroxetine hydrochloride patents." (Pl. Opp. at 9-10.)

Upon consideration of the parties' arguments, the Court is not persuaded that a transfer to the Northern District of Illinois would be appropriate. Discovery in the Illinois Action has been completed, thus diminishing the possibility of consolidation or coordination to promote judicial economy. Moreover, Geneva does not suggest that any of its witnesses might be unavailable for trial in this district. *See Jumara*, 55 F.3d at 879 (stating that relevant private interests include "the convenience of the witnesses--but only to the extent that the witnesses may actually be unavailable for trial in one of the fora."). Most significantly, although both this action and the Illinois action involve the '723 patent, this action also involves two other patents which are not at issue in the Illinois litigation. It is not enough for Geneva to suggest, without any evidence to support its assertion, that "[t]he Apotex paroxetine hydrochloride product and the Geneva paroxetine hydrochloride product must be similar, even identical, in many respects, to meet the Food and Drug Administration's requirements to be approved as generic versions of the paroxetine hydrochloride product...." (Def. Mem. at 5.) Because the relevant factors do not strongly favor a transfer, SmithKline's choice of forum must prevail. Accordingly, Geneva's Motion to Transfer is denied. An Order follows.

ORDER

AND NOW, this 11 th day of February, 2000, upon consideration of Defendant's Motion to Transfer (docket # 9), Plaintiffs' Opposition to the Motion to Transfer (docket # 10), and Defendant's Reply to Plaintiffs' Opposition (docket # 11), it is ORDERED that the Motion to Transfer is DENIED.

Not Reported in F.Supp.2d, 2000 WL 217642 (E.D.Pa.)

END OF DOCUMENT

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Attorneys for the Plaintiff

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

PFIZER INC., PHARMACIA & UPJOHN COMPANY LLC, and PFIZER HEALTH AB,.	**Civil Action No. 07-11198-LTS(KNF)**
Plaintiff,	**DECLARATION OF JAMES S. TRAINOR, JR.**
v.	
TEVA PHARMACEUTICALS USA, INC.,	
Defendant.	

I, James S. Trainor, Jr., declare as follows:

1. I am an attorney at law duly authorized and admitted to practice law before this Court. I am an associate with the law firm of White & Case LLP, counsel for Plaintiffs Pfizer Inc., Pharmacia & Upjohn Company LLC, and Pfizer Health AB ("Pfizer). I have knowledge of the facts set forth in this Declaration and, if called as a witness, could competently testify to these facts.

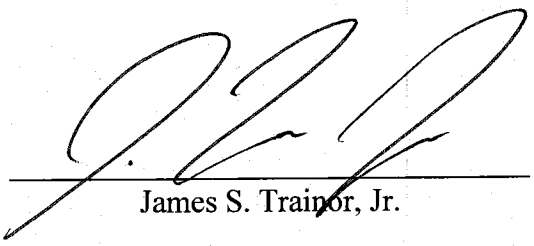
2. I represent Pfizer in Pfizer, Inc. v. Teva Pharms. USA, Inc., No. 07-0174 (DMC)(MF) (D.N.J. 2007). In conjunction with my representation of Pfizer in that action, I have regularly corresponded with attorneys from Goodwin Procter, LLP, counsel for Defendant Teva Pharmaceuticals USA, Inc. ("Teva"), regarding discovery.

3. Attached hereto as **Exhibit 1** is a true and correct copy of the current scheduling order in the New Jersey action. Although the stipulated deadline for Teva's production was December 21, 2007, Teva has yet to produce certain documents called for under the order.

4. Attached hereto as **Exhibit 2** is a true and correct copy of an email to Alison Hanstead of White & Case from Elaine Hermann Blais of Goodwin Procter. This email evidences Teva's stated intention to complete its document production in the New Jersey action by February 1, 2008.

5. On January 11, 2008, I participated in a teleconference with counsel for Teva/Ivax. During that teleconference, Ms. Blais communicated her agreement, on behalf of her clients, to extend all dates in the scheduling order of Exhibit 1 for times commensurate with Teva/Ivax's delay in finalizing its document production in the New Jersey action. Accordingly, the last date on the schedule of Exhibit 1 - the deadline for filing summary judgment briefs - will be extended for a period of time that is yet to be determined but will, in no event, fall earlier than April 18, 2008.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this Declaration was executed in New York, New York on January 31, 2008.



James S. Trainor, Jr.

EXHIBIT 1

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB, Plaintiffs, v. IVAX PHARMACEUTICALS, INC., Defendant.	**C. A. No. 07-0174 (DMC) (MF)**
IVAX PHARMACEUTICALS, INC. and TEVA PHARMACEUTICALS USA, INC., Counterclaim-Plaintiffs, v. PFIZER INC., PHARMACIA & UPJOHN COMPANY, and PFIZER HEALTH AB, Counterclaim-Defendants.	

STIPULATED ORDER EXTENDING DISCOVERY SCHEDULE

THIS MATTER having come before the Court upon the joint application of Plaintiffs and Counterclaim-Defendants Pfizer, Inc., Pharmacia & Upjohn Company, and Pfizer Health AB (collectively, "Pfizer"), Defendant and Counterclaim-Plaintiff IVAX Pharmaceuticals, Inc. ("IVAX"), and Counterclaim-Plaintiff Teva Pharmaceuticals USA, Inc. ("Teva") to extend the discovery schedule in this action, all having consented to the terms of this Stipulated Order,

IT IS HEREBY ORDERED THAT:

1. The parties shall proceed in this action according to the following schedule:

EVENT	COMPLETION DATE
Teva and IVAX produce documents regarding Detrol LA responsive to Pfizer's Document Request Nos.	December 21, 2007

71, 72, 74, 76, 77, and 79 to IVAX, and Document Request Nos. 27, 28, 30, and 31 to Teva	
Supplemental Expert Reports, if any, Due	January 22, 2008
Responding Expert Reports, if any, Due	February 5, 2008
Expert Depositions, if any, Complete	February 19, 2008
Summary Judgment Motions Due	March 7, 2008

STIPULATED AND AGREED TO:

Dated: November 20, 2007

LITE DEPALMA GREENBERG & RIVAS, LLC

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Attorneys for Pfizer Inc., Pharmacia & Upjohn Company, and Pfizer Health AB

IT IS HEREBY SO ORDERED.

Dated: 11/27/07

Honorable Mark Falk, U.S.M.J.

161914 v1

EXHIBIT 2

Hanstead, Alison

From: Blais, Elaine Herrmann [eblais@goodwinprocter.com]
Sent: Thursday, January 24, 2008 1:18 PM
To: Hanstead, Alison
Cc: Mitrokostas, Nicholas K; Garko, Sheryl Koval
Subject: RE: Pfizer v. IVAX (Detrol)

Alison,

We are in the process of preparing another set of documents for production and expect to send them out to you tomorrow. The remaining documents are nearly all spreadsheets. We expect to send you the remainder of the production next Friday, February 1.

We expect to respond to the remaining issues raised in your December 13th letter tomorrow.

Elaine

Elaine Herrmann Blais
Goodwin | Procter LLP
Exchange Place
Boston, MA 02109-2881
Tel: (617) 570-1205
Fax: (617) 523-1231
eblais@goodwinprocter.com

From: Hanstead, Alison [mailto:ahanstead@ny.whitecase.com]
Sent: Wednesday, January 23, 2008 6:43 PM
To: Blais, Elaine Herrmann
Subject: Pfizer v. IVAX (Detrol)

Elaine,

I am writing to follow up on Teva and IVAX's document production. Please let me know if we can expect additional documents this week. Also, please let me know if you have an estimated completion date for the document production.

Also, we have not yet received a response to all of the requests set forth in my December 13th letter. Please let me know when we can expect a response to the outstanding requests.

Regards,
Alison

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